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### Research Article

We previously reported that prostaglandin E2 (PGE2) at a physiologic concentration ( $10^{-8}$  M) and interferon gamma (IFN gamma), acting sequentially, were required for the differentiation of suppressor cells in mitogen-stimulated cultures. The present study was designed to test whether PGE2 might mediate IFN gamma-dependent effects on CD8+ cells by altering the number and/or affinity of their IFN gamma receptors. CD8+ and CD4+ cells when cultured for 18 h expressed comparable numbers of IFN gamma receptors of a single high affinity. Incubation with  $10^{-8}$  M PGE2 for 18 h, however, increased the number of IFN gamma receptors on CD8+ cells without affecting the binding affinity. Similar effects were not observed with CD4+ cells, nor when CD8+ cells were cultured in  $10^{-8}$  M PGD2. Concentrations of PGE2, which were ineffective in the induction of IFN gamma-dependent suppressor cell differentiation, also did not affect IFN gamma receptor expression on CD8+ cells. This observation of a specific stimulatory effect of PGE2 on the display of IFN gamma receptors of CD8+ cells suggests a novel mechanism for eicosanoid function through tissue-specific regulation of hormone receptors.

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## Prostaglandin E<sub>2</sub> Selectively Increases Interferon Gamma Receptor Expression on Human CD8<sup>+</sup> Lymphocytes

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### Abstract

We previously reported that prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) at a physiologic concentration (10<sup>-8</sup> M) and interferon gamma (IFN $\gamma$ ), acting sequentially, were required for the differentiation of suppressor cells in mitogen-stimulated cultures. The present study was designed to test whether PGE<sub>2</sub> might mediate IFN $\gamma$ -dependent effects on CD8<sup>+</sup> cells by altering the number and/or affinity of their IFN $\gamma$  receptors. CD8<sup>+</sup> and CD4<sup>+</sup> cells when cultured for 18 h expressed comparable numbers of IFN $\gamma$  receptors of a single high affinity. Incubation with 10<sup>-8</sup> M PGE<sub>2</sub> for 18 h, however, increased the number of IFN $\gamma$  receptors on CD8<sup>+</sup> cells without affecting the binding affinity. Similar effects were not observed with CD4<sup>+</sup> cells, nor when CD8<sup>+</sup> cells were cultured in 10<sup>-8</sup> M PGD<sub>2</sub>. Concentrations of PGE<sub>2</sub>, which were ineffective in the induction of IFN $\gamma$ -dependent suppressor cell differentiation, also did not affect IFN $\gamma$  receptor expression on CD8<sup>+</sup> cells. This observation of a specific stimulatory effect of PGE<sub>2</sub> on the display of IFN $\gamma$  receptors of CD8<sup>+</sup> cells suggests a novel mechanism for eicosanoid function through tissue-specific regulation of hormone receptors.

### Introduction

Both PGE<sub>2</sub> and IFN $\gamma$  play roles in downregulation of the immune response. Data from several laboratories suggest that these agents act in large measure through induction of T suppressor cells that suppress many manifestations of T lymphocyte function including mitogen responsiveness (1–5). Previously we reported that differentiation of T suppressor cells in pokeweed mitogen (PWM) stimulated cultures required PGE<sub>2</sub> plus IFN $\gamma$ , acting in sequence, for the generation of T suppressor cells (6, 7). That is, treatment with PGE<sub>2</sub> was required first, followed by IFN $\gamma$ . Our preliminary studies also indicated that CD8<sup>+</sup> cells treated with PGE<sub>2</sub> bound greater quantities of IFN $\gamma$  than cells treated with medium alone. These observations suggested possible effects of PGE<sub>2</sub> on IFN $\gamma$  receptor expression.

A single high affinity IFN $\gamma$  receptor has been described on both cultured and resting human T cells (8, 9). Upon activation of T lymphocytes, however, the number of IFN $\gamma$  receptors has been reported to decrease by twofold (10). Since previous studies demonstrated that biological responses of IFN $\gamma$  directly correlated with the amount of IFN $\gamma$  bound to its specific cell receptors (8), the present study was designed to explore possible differences in the regulation of IFN $\gamma$  receptors of CD8<sup>+</sup> and CD4<sup>+</sup> cells in response to PGE<sub>2</sub>. Such differences may relate to the initial PGE<sub>2</sub> requirement of CD8<sup>+</sup> cells in the IFN $\gamma$ -dependent differentiation of T suppressor cells.

### Methods

**Leukocytes.** Peripheral blood mononuclear cells (PBMC) were obtained from heparinized whole blood. Some of the cells were stored in liquid nitrogen in 7.5% dimethyl sulfoxide until used.

**Reagents.** Monoclonal antibodies were obtained from Ortho Diagnostic Corp. (Raritan, NJ), Coulter Immunology (Hialeah, FL), and Becton Dickinson Monoclonal Center, Inc. (Mountain View, CA). Anti-CD28 MAb 9.3 (11), was kindly supplied by Dr. J. A. Hansen (Puget Sound Blood Center, Seattle, WA). Prostaglandins were purchased from Sigma Chemical Co. (St. Louis, MO) and human recombinant IFN $\gamma$  was purchased from Genzyme (Boston, MA) and Amgen Biologicals (Thousand Oaks, CA).

**<sup>125</sup>I-IFN $\gamma$  labeling.** rIFN $\gamma$  was radiolabeled using the Boulton-Hunter reagent (New England Nuclear, Boston, MA) as previously described (12). Unconjugated iodine was separated from protein-bound iodine over a Sephadex G-25 fine column (Pharmacia Fine Chemicals, Piscataway, NJ). Iodinated rIFN $\gamma$  eluted from the gel column as a dimer with a *M<sub>r</sub>* of ~ 34,000. The initial specific activity of the <sup>125</sup>I-IFN $\gamma$  of different preparations varied between 18 and 34  $\mu$ Ci/ $\mu$ g, as counts per minute per microgram of biologically active IFN $\gamma$ . IFN $\gamma$  activity of radiolabeled preparations was measured by their ability to protect WISH cells (human amnion cell line CCL23; American Type Culture Collection, Rockville, MD) from lysis by vesicular stomatitis virus.

**T cell separation and analysis.** Techniques for fractionation of PBMC into subpopulations have been previously described (6). Briefly, fresh PBMC were depleted of adherent cells by plastic adherence. Nonadherent cells were further separated into B and T cell populations by passing over nylon wool columns. Purified CD4<sup>+</sup> and CD8<sup>+</sup> cell populations were prepared from the T cell-enriched fractions (nylon wool nonadherent cells) by negative selection using MAb and C treatment. Indirect immunofluorescence analysis indicated < 5% contamination with T cells of the reciprocal phenotype. In some experiments CD8<sup>+</sup> cells were further fractionated by panning into CD28<sup>-</sup> and CD28<sup>+</sup> subpopulations; flow cytometric analysis showed that positively selected cells were > 90% positive and negatively selected cells were < 5% positive for the antigen. Cell size was determined using forward angle light scatter on a Coulter EPICS V flow cytometer.

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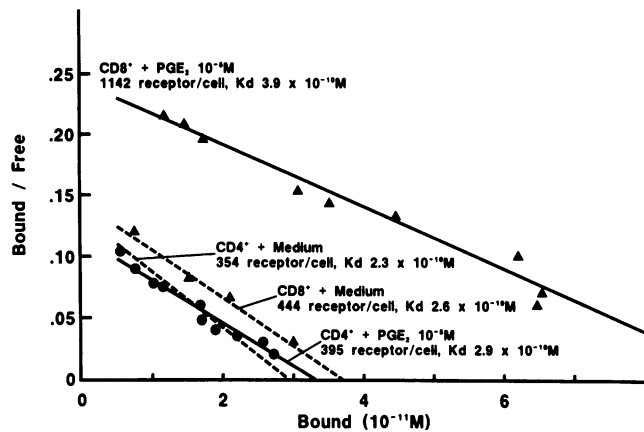


Figure 1.  $10^{-8}$  M  $PGE_2$  selectively increases the number of  $IFN\gamma$  receptors on  $CD8^+$  cells.  $CD8^+$  cells were cultured in medium (—●—) or  $10^{-8}$  M  $PGE_2$  (—▲—) for 18 h at  $37^\circ C$ .  $CD4^+$  cells from the same donor were similarly cultured in medium (—●—) or  $10^{-8}$  M  $PGE_2$  (—■—).

**Cell cultures.**  $2-3 \times 10^6$   $CD8^+$  or  $CD4^+$  cells/ml were cultured in RPMI 1640 supplemented with 10% pooled human AB<sup>+</sup> heat-inactivated serum, 2 mM glutamine, 100  $\mu g/ml$  streptomycin, and 100 U/ml penicillin. The cells were incubated at  $37^\circ C$  in 5%  $CO_2$  for 18 h and then washed twice with RPMI containing 2% pooled human AB<sup>+</sup> heat-inactivated serum.

**$^{125}I$ - $IFN\gamma$  binding assay.** The binding assay was performed according to published protocols (12). Briefly, the cells were resuspended in RPMI 1640 supplemented with 2 mM glutamine and 2% pooled human AB<sup>+</sup> heat-inactivated serum. Duplicates of samples of a fixed number of lymphocytes were incubated with increasing concentrations of radiolabeled r $IFN\gamma$  in Eppendorf tubes for 2 h at  $4^\circ C$  with occasional shaking. The cells were then washed twice using cold medium, and layered over a cushion of phthalate oils. After centrifugation, the radioactivity in the cell pellet was measured. Nonspecific binding, assessed by measuring the binding of  $^{125}I$ - $IFN\gamma$  in the presence of a 200–400-fold excess of unlabeled r $IFN\gamma$ , varied between 10 and 33% of total isotope bound. Computer analysis of the best fit for the data points was performed using the Grapher program (Golden Software Inc., Golden, CO). Data in the figures represent the calculated specific binding per  $5 \times 10^6$  cells in 0.1 ml. Specific binding was analyzed using the method of Scatchard (13). Statistical analysis of the data was performed using paired-sample  $t$  tests with two-tailed hypotheses and Bonferroni's method to adjust for multiple comparisons (14).

## Results

**Effect of prostaglandin  $E_2$  on the number of  $IFN\gamma$  receptors of  $CD8^+$  and  $CD4^+$  cells.** We previously reported that  $10^{-8}$  M  $PGE_2$ , a concentration that falls in the physiological range (15), induced  $IFN\gamma$ -dependent differentiation of  $CD8^+$  suppressor cells (7). We therefore investigated whether treatment of  $CD8^+$  and  $CD4^+$  cells with  $PGE_2$  at this concentration would affect the number and/or affinity of  $IFN\gamma$  receptors. Purified  $CD8^+$  cells and  $CD4^+$  cells obtained from the same donor were cultured in medium alone or in  $10^{-8}$  M  $PGE_2$  for 18 h. Scatchard analysis of  $IFN\gamma$  specific binding resulted in linear plots (Fig. 1); the calculated number of  $IFN\gamma$  receptors/ $CD8^+$  cell cultured in medium ranged from 315 to 399 (Table I). After treatment with  $10^{-8}$  M  $PGE_2$ , however, the number of  $IFN\gamma$  receptors was significantly increased. In marked contrast to the effect on  $CD8^+$  cells, treatment of  $CD4^+$  cells with  $10^{-8}$

Table I. Effect of  $PGE_2$  on Expression of  $IFN\gamma$  Receptors on  $CD8^+$  and  $CD4^+$  Lymphocytes

Lymphocyte subset	No. of experiments	18-h culture	Receptors/cell*	$K_d \times 10^{-10}$ M*
A $CD8^+$	5	Medium	$367 \pm 64$	$3.0 \pm 1.2$
$CD8^+$	3	$PGE_2$ $10^{-6}$ M	$509 \pm 109$	$4.5 \pm 1.7$
$CD8^+$	5	$PGE_2$ $10^{-8}$ M	$1,089 \pm 187^\dagger$	$4.2 \pm 1.4$
$CD8^+$	3	$PGE_2$ $10^{-10}$ M	$427 \pm 146$	$3.9 \pm 2.0$
$CD8^+$	3	$PGE_2$ $10^{-8}$ M	$426 \pm 170$	$4.2 \pm 2.1$
B $CD4^+$	4	Medium	$308 \pm 36$	$2.5 \pm 0.5$
$CD4^+$	3	$PGE_2$ $10^{-6}$ M	$332 \pm 126$	$3.2 \pm 1.8$
$CD4^+$	4	$PGE_2$ $10^{-8}$ M	$340 \pm 98$	$3.7 \pm 1.7$
$CD4^+$	2	$PGE_2$ $10^{-10}$ M	$357$ (264, 450)	$2.1$ (1.3, 3.0)

\* Mean  $\pm$  SD or mean (range).

$^\dagger$  Statistically significant ( $P < 0.012$ ).

M  $PGE_2$  did not significantly change the number of  $IFN\gamma$  receptors. We reported previously that  $10^{-8}$  M  $PGD_2$  unlike  $PGE_2$ , could not replace the  $PGE_2$  signal in  $IFN\gamma$ -dependent T suppressor differentiation (7). Similarly, when  $CD8^+$  cells were treated with  $10^{-8}$  M  $PGD_2$  rather than  $PGE_2$  there was no effect on expression of  $IFN\gamma$  receptors (Table I).

**Dose-response analysis of  $PGE_2$  effects on  $IFN\gamma$  receptor expression of  $CD8^+$  and  $CD4^+$  cells.** Unlike  $10^{-8}$  M  $PGE_2$ , higher ( $10^{-6}$  M) and lower ( $10^{-10}$  M) concentrations of  $PGE_2$  failed to cause  $IFN\gamma$ -dependent differentiation of  $CD8^+$  suppressor cells (7). We therefore examined whether the stimulatory effect of the  $10^{-8}$  M concentration on  $IFN\gamma$  receptor expression could be observed at these concentrations. Purified  $CD8^+$  and  $CD4^+$  cells were cultured in medium alone or in  $10^{-6}$ ,  $10^{-8}$ , or  $10^{-10}$  M concentrations of  $PGE_2$  for 18 h. As shown in Fig. 2 and Table I, the stimulatory effect of  $PGE_2$  on  $IFN\gamma$  receptors of  $CD8^+$  cells was exhibited only at the  $10^{-8}$  M concentration. At no concentration tested was the affinity of the receptors significantly affected nor was the size of the cells altered compared to cells cultured in medium alone (data not shown), leading us to conclude that the observed increase in binding to  $CD8^+$  cells was the result of increased numbers of

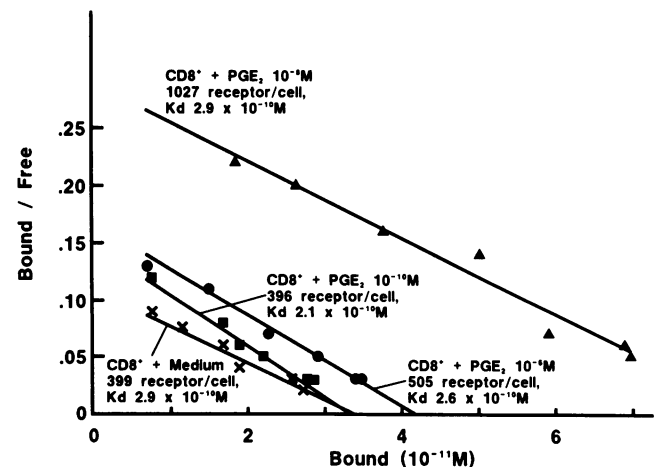


Figure 2. Dose-response analysis of the effect of  $PGE_2$  on  $IFN\gamma$  receptors of  $CD8^+$  cells.  $CD8^+$  cells were cultured for 18 h at  $37^\circ C$  in medium (×),  $10^{-6}$  M (●),  $10^{-8}$  M (▲), or  $10^{-10}$  M (■) concentrations of  $PGE_2$ .

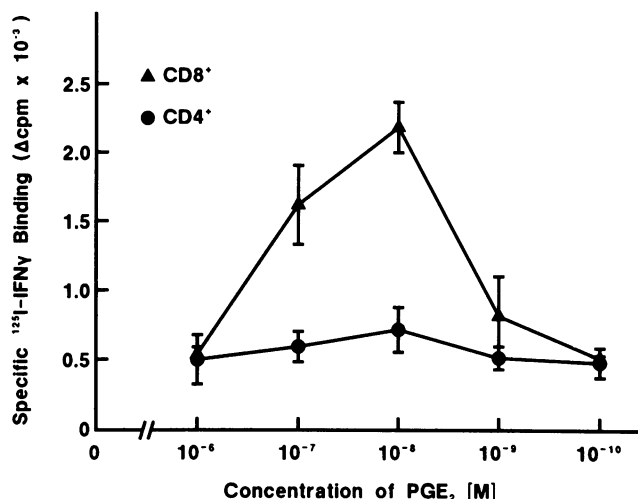


Figure 3. Effects of varying concentrations of PGE<sub>2</sub> on specific binding of <sup>125</sup>I-IFN $\gamma$  to CD8<sup>+</sup> and CD4<sup>+</sup> cells. CD8<sup>+</sup> ( $\Delta$ ) and CD4<sup>+</sup> ( $\bullet$ ) cells were cultured in increasing concentrations of PGE<sub>2</sub> for 18 h at 37°C. Each binding activity represents the mean  $\pm$  SD of triplicate measurements of specific binding of a single concentration of <sup>125</sup>I-IFN $\gamma$  to  $5 \times 10^6$  cell. Using two donors, we performed the experiment twice with similar results.

IFN $\gamma$  receptors. No significant effects of PGE<sub>2</sub> were observed on CD4<sup>+</sup> cells at any concentration tested (Table I), confirming the selective effect of PGE<sub>2</sub> on IFN $\gamma$  receptors of CD8<sup>+</sup> cells. It was not technically feasible to establish more extensive dose-response curves for both CD4<sup>+</sup> and CD8<sup>+</sup> cells in the same experiment using saturation binding curves for each PGE<sub>2</sub> concentration tested. Therefore, we compared the mean of triplicate measurements of specific binding of a single concentration of <sup>125</sup>I-IFN $\gamma$  to cells treated with increasing concentration of PGE<sub>2</sub> for 18 h. As demonstrated in Fig. 3 the maximal effect of PGE<sub>2</sub> appeared at 10<sup>-8</sup> M concentration, and at lower or higher concentrations the binding declined towards control levels.

**IFN $\gamma$  receptor expression on CD8<sup>+</sup> subpopulations.** Expression of CD28, identified by the MAb 9.3, has been reported as a phenotypic marker of CD8<sup>+</sup> cytotoxic lymphocytes (CTL), but not CD8<sup>+</sup> T suppressor lymphocytes (11). Our earlier studies similarly demonstrated that the suppressor-effector activity of PWM-activated CD8<sup>+</sup> cells was predominantly in the CD28<sup>-</sup> subpopulation of CD8<sup>+</sup> cells (6). We therefore investigated whether PGE<sub>2</sub> had a preferential stimulatory effect on CD8<sup>+</sup> CD28<sup>-</sup> versus CD8<sup>+</sup> CD28<sup>+</sup> cells. Analysis of Scatchard plots of CD8<sup>+</sup> cells cultured in medium alone or in PGE<sub>2</sub> 10<sup>-8</sup> M for 18 h and then fractionated into CD28<sup>+</sup> and CD28<sup>-</sup> subpopulations revealed an increase in IFN $\gamma$  receptors on both subsets (Fig. 4 and Table II), leading us to conclude that these two subsets of CD8<sup>+</sup> lymphocytes did not differ significantly in their responses to this treatment.

## Discussion

This manuscript describes a PGE<sub>2</sub>-induced increase in receptors for IFN $\gamma$  that was selective for CD8<sup>+</sup> lymphocytes. Since PHA-stimulation of T cells results in downregulation of IFN $\gamma$  receptors (10), the selective stimulatory effect of 10<sup>-8</sup> M PGE<sub>2</sub>

may represent a crucial difference between CD4<sup>+</sup> and CD8<sup>+</sup> cells in the regulation of IFN $\gamma$  receptors and ultimately in their differentiation. Supporting this hypothesis, previous studies have shown that biological responses of IFN $\gamma$  directly correlate with the amount of IFN $\gamma$  bound to specific cell receptors (8). Furthermore, dexamethasone has been shown to increase levels of IFN $\gamma$  receptors on monocytes and to enhance IFN $\gamma$  functions (16). As noted, we have also shown that IFN $\gamma$ -induced differentiation of PGE<sub>2</sub>-treated CD8<sup>+</sup> cells exhibited a dose dependence (7) similar to that for increased receptor expression.

Little is known about the regulation of IFN $\gamma$  receptors, however, there are data in other systems that may be relevant to our findings. For example, Akahoshi et al. recently reported that interleukin-1 (IL1) stimulates its own receptor expression on human fibroblasts through the endogenous production of PGE<sub>2</sub> (17). These authors also reported that addition of exogenous PGE<sub>2</sub> or analogues of AMP increased the specific binding of <sup>125</sup>I-labeled human IL-1 $\alpha$  by more than twofold without affecting the binding affinity. Analogous to our results, the augmented IL1 receptor expression was maximal after 18 h incubation (17). The PGE<sub>2</sub> effect on IL1 receptors, however, was observed in a dose-dependent manner and was maximal at the supraphysiological concentration of 10<sup>-6</sup> M (17). A role for a monocyte-secreted product in the differential expression of IL2 receptors on helper and suppressor T cells, which could not be replaced by IL1, was also reported by Malek et al. (18). In these studies, a monocyte-mediated signal induced expression of IL2 receptors on CD4<sup>+</sup> helper T cells, but not on CD8<sup>+</sup> suppressor cells. Since monocytes are major producers of PGEs, a role for PGs in this process is also possible. In addition, treatment with IFN $\gamma$  which, like PGE<sub>2</sub>, is a potent inducer of cAMP, increases expression of cellular receptors for tumor necrosis factor, IL2 and IgG Fc receptor (19).

Although we observed selectivity of PGE<sub>2</sub> effects on CD8<sup>+</sup> versus CD4<sup>+</sup> cells, similar selective effects were not observed among CD8<sup>+</sup> subpopulations defined by expression of CD28.

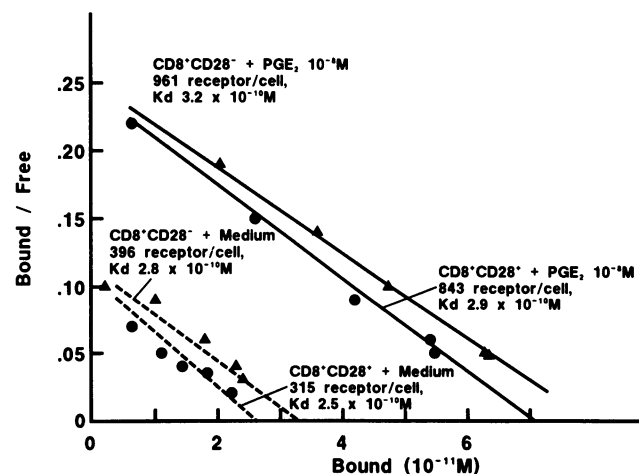


Figure 4. Effect of PGE<sub>2</sub> on IFN $\gamma$  receptor expression on CD8<sup>+</sup> subpopulations. CD8<sup>+</sup> cells were cultured in medium alone or in PGE<sub>2</sub>. Cells cultured in medium were then fractionated by panning into CD28<sup>+</sup> ( $\bullet$ ) and CD28<sup>-</sup> ( $\Delta$ ) subpopulations. Similarly, CD8<sup>+</sup> cells cultured in 10<sup>-8</sup> M PGE<sub>2</sub> were fractionated by panning into CD28<sup>+</sup> ( $\bullet$ ) and CD28<sup>-</sup> ( $\Delta$ ) subpopulations.

Table II. Expression of IFN $\gamma$  Receptors on CD8<sup>+</sup>CD28<sup>-</sup> and CD8<sup>+</sup>CD28<sup>+</sup> Subpopulations in Response to 10<sup>-8</sup> M PGE<sub>2</sub>

Lymphocyte subset	No. of experiments	18-h Culture	Receptors/cell*	K <sub>d</sub> × 10 <sup>-10</sup> M*
CD8 <sup>+</sup> CD28 <sup>+</sup>	2	Medium	302 (289; 315)	2.9 (2.5; 3.2)
CD8 <sup>+</sup> CD28 <sup>-</sup>	2	Medium	346 (295; 396)	3.5 (2.8; 4.1)
CD8 <sup>+</sup> CD28 <sup>+</sup>	2	PGE <sub>2</sub> 10 <sup>-8</sup> M	883 <sup>†</sup> (843; 922)	3.7 (2.9; 4.5)
CD8 <sup>+</sup> CD28 <sup>-</sup>	2	PGE <sub>2</sub> 10 <sup>-8</sup> M	982 <sup>†</sup> (961; 1002)	2.5 (1.9; 3.2)

\* Mean (range). <sup>†</sup> Statistically significant ( $P < 0.03$ ).

An interesting possibility is that the increase in IFN $\gamma$  receptors on the surface of CD8<sup>+</sup> CD28<sup>+</sup> cells is related to the stimulatory effect of IFN $\gamma$  on differentiation of CD8<sup>+</sup> cytotoxic cells (20), perhaps reflecting the dual effects on this process of agents that increase intracellular cAMP concentrations (21). An increase in cAMP in the first 12 to 24 h of cultures enhanced CTL activity, whereas CTL generation was inhibited when intracellular cAMP concentrations were elevated for longer than 24 h (21). Thus, the early enhancement of CTL activity by an increase in cAMP correlates with the reported 24-h life span of PGE<sub>2</sub> receptors on the surface of lymphocytes (22), with our observation that PGE<sub>2</sub> increased IFN $\gamma$  binding to CD8<sup>+</sup> cells and with the stimulatory effect of IFN $\gamma$  on CTL generation (20). The reason that we (7) and others (3) failed to observe differentiation of CTL in response to PGE<sub>2</sub> treatment may reflect the ability of PGE<sub>2</sub> to inhibit IL2 production (1), which is required in this process (20). Our findings may also indicate differential responses of CD8<sup>+</sup> CD28<sup>-</sup> and CD8<sup>+</sup> CD28<sup>+</sup> subpopulations to intracellular events occurring subsequent to PGE<sub>2</sub> binding. For example, it is possible that the differences in the suppressor-effector function of these two subpopulations reflect a difference in the amounts of cAMP generated in response to IFN $\gamma$  or in the response of these two subpopulations to an increase in cAMP. Indeed the studies of Goodwin et al. (23) indicate that T lymphocyte subsets differ in responses to agents that increase cAMP, such as IFN $\gamma$  (24), with greater increases in cAMP levels of T suppressor cells as compared to T helper cells.

This study provides new insights into mechanisms of action of a class of arachidonic acid metabolites that is known for its important modulatory effects on a broad range of physiologic responses. The evidence for tissue-specific differences in the consequences of eicosanoids on hormonal receptors may have important implications for other systems affected by these agents and may lead to clearer understanding of the diversity of their immunoregulatory activities.

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