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Interferon Enhancement of HLA-DR Antigen Expression on Epidermal Langerhans Cells

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Langerhans cells (LCs) are dendritic epidermal cells whose ability to function as accessory/stimulatory cells in initiating the immune response is, like that of macrophages, dependent on the expression of class II major histocompatibility antigens. In normal human skin approximately 50% of LCs identified by cell surface T6 antigenicity also express HLA-DR histocompability determinants. We report here that recombinant DNA-derived human interferon (IFN)-gamma, but not IFN-alpha$_2$, induces the expression of HLA-DR antigens by the population of human epidermal LCs on which such antigens normally are not detected. IFN-gamma effectively induced HLA-DR on both neonatal and adult epidermal LCs and such induction was blocked by neutralization with a murine monoclonal antibody to IFN-gamma. IFN-gamma induction of LC HLA-DR expression is inhibited by prostaglandin E_2 (PGE_2) and is mimicked by the presence of fatty acid cyclooxygenase inhibitors, known to reduce PGE_2 production. These results suggest that IFN-gamma may play a role in regulating skin-associated immune responses through enhanced expression of HLA-DR antigens on LCs and that such enhancement may be mediated by alterations in arachidonic acid metabolism.

The major histocompatibility complex encodes for two classes of cell surface glycoproteins. In humans these membrane proteins are class I (HLA-A, B, C) and class II (HLA-DR, DS, SB) molecules [1–3]. In contrast to class I antigens which are expressed upon most somatic cells except adult erythrocytes, class II antigens have a restricted cellular distribution. The most extensively studied class II antigen, HLA-DR, for example, is normally expressed only by B cells and accessory cells such as monocytes, macrophages, dendritic cells, and Langerhans cells (LCs) [4–7]. HLA-DR molecules are homologous structurally and functionally with murine Ia surface glycoproteins [8], and are functionally important in that their expression is required for accessory cells to present nominal antigen to helper T cells and initiate the immune response [9–13]. HLA-DR molecules are also important as stimulatory antigens in triggering mixed lymphocyte reactions [9] and mixed epidermal cell–lymphocyte reactions [12,13].

Several studies in both the human and murine systems have indicated that expression of DR/Ia antigens upon B cells and macrophages can be stimulated by soluble products of activated T cells [14–17]. Specifically, recent studies have identified the DR/Ia inducing lymphokine as interferon (IFN)-gamma, and have shown that IFN-gamma produced from the cloned IFN-gamma gene is capable of such DR/Ia induction [18–20]. Both IFN-alpha and IFN-beta appear to be either less effective or ineffective as DR/Ia inducers [21,22].

LCs, which are derived from bone marrow precursor cells [23] and reside within the epidermis, share many characteristics with macrophages inducing DR/Ia expression [6,7] and accessory cell functions [10–13,24]. LCs are the only cells in the normal human epidermis to express DR-antigen and the cell surface antigen T6, a molecule also found on 70% of human thymocytes [25]. Just as not all macrophages express DR antigens, using immunofluorescent microscopic techniques, we and others have found that approximately 50% of T6 bearing LCs do not express detectable levels of DR antigens [26–28]. In this study we report a selective enhancement of HLA-DR expression on human epidermal LCs that is effected by exposure to recombinant DNA-derived IFN-gamma, but not to IFN-alpha$_2$.

The intracellular mechanisms responsible for IFN-gamma induction of DR/Ia antigens are unknown, but studies with murine macrophages suggest that products of the arachidonic acid cascade are involved as prostaglandins of the E series (PGE) were reported to inhibit lymphokine-induced Ia expression [18,29]. Moreover, the cyclooxygenase inhibitor, indomethacin, mimicked lymphokine action by inducing macrophage Ia expression by itself [29]. Similarly, we report here that PGE_2 inhibits the IFN-gamma induced HLA-DR expression on LCs and further demonstrate that indomethacin and 3 other cyclooxygenase inhibitors can mimic IFN-gamma action by increasing HLA-DR expression on LCs.

MATERIALS AND METHODS

Interferons and Anti-Interferons

Human recombinant IFN-alpha$_2$ (6.6×10^7 units/ml) from *Escherichia coli* was kindly supplied by Schering Corporation, Kenilworth, New Jersey. Human recombinant *E. coli*-derived IFN-gamma (1.0×10^7 units/ml) and murine monoclonal antibody (IgG_1) to human IFN-gamma (5×10^4 neutralizing units/ml) were kindly supplied by Genentech, Inc., South San Francisco, California.

Chemicals

PGE_2, thromboxane B_2 (TXB_2), indomethacin, nordihydroguaiaretic acid (NDGA), and imidazole were obtained from Sigma Chemical, St. Louis, Missouri. Benoxaprofen and 5,8,11,14-eicosatetraynoic acid (ETYA) were obtained from Eli Lilly, Inc., Indianapolis, Indiana and Hoffmann-LaRoche, Inc., Nutley, New Jersey. PGE_2, TXB_2, and indomethacin were dissolved in absolute ethanol and diluted in RPMI–10% heat-inactivated fetal calf serum (ΔFCS) to the final tested concentrations. At the dilutions tested ethanol had no effect on HLA-

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Abbreviations:
ETYA: 5,8,11,14-eicosatetraynoic acid
ΔFCS: heat-inactivated fetal calf serum
HLA: human leukocyte antigen
IFN: interferon
LC(s): Langerhans cell(s)
NDGA: nordihydroguaiaretic acid
PGE_2: prostaglandin E_2
TXB_2: thromboxane B_2

DR expression. Benoxaprofen, ETYA, and NDGA were dissolved in minimal amounts of 1 N NaOH, immediately neutralized with 1 N HCl, and diluted (as was imidazole directly) in RPMI–10% ΔFCS to the final concentrations desired.

Dispersed Epidermal Cell Cultures

Dispersed epidermal cells (5×10^5) isolated from neonatal human foreskin as described in [7], were maintained in vitro at 37°C for 20 h in humidified 5% CO_2 in 2.0 ml RPMI-1640 containing 10% ΔFCS and the indicated concentrations of either pure, *E. coli* recombinant DNA derived human IFN-alpha$_2$, IFN-gamma, or other compounds as indicated. Dispersed epidermal cells from adult facial skin were isolated and maintained as indicated above in 3 separate experiments.

Detection of LC Surface Antigens HLA-DR and T6 on Dispersed Epidermal Cells

Simultaneous detection of HLA-DR and T6 antigen-bearing cells was achieved under epifluorescent microscopy following sequential treatment of the epidermal cells with mouse monoclonal anti-HLA-DR IgG, (Ortho Diagnostics, Raritan, New Jersey), rhodaminated goat antimouse IgG (Meloy Labs, Springfield, Virginia), mouse monoclonal anti-T1 IgG (to saturate free antimouse IgG binding sites), and fluoresceinated mouse monoclonal anti-T6 IgG (Ortho Diagnostics) [26]. Epidermal cells were examined as wet mounts under epifluorescent microscopy with appropriate excitatory and barrier filters and the mean number, and SD, of $DR^+/T6^+$ cells were calculated.

Skin Explant Incubation In Vitro

Four millimeter-diameter specimens of freshly excised human neonatal foreskin, trimmed of fat and dermis, were maintained in vitro under conditions identical to those described for dispersed epidermal cells. After 20 h in culture, intact epidermal sheets were prepared from each specimen following incubation in 1 N NaBr at 37°C for 60 min. Adult facial skin prepared and maintained under these conditions was utilized in 2 separate experiments.

Detection of HLA-DR Bearing LC in Epidermal Sheets

Epidermal sheets were incubated with either mouse monoclonal anti-HLA-DR IgG or anti-T6 IgG (Ortho Diagnostics) followed by incubation with fluoresceinated goat antimouse IgG (Meloy Labs), at 23°C [26]. The number of fluorescing, dendritic cells in ten 400 × fields was counted under epifluorescent microscopy and a mean and SEM per mm^2 calculated.

Statistics

The statistical difference between means was calculated using the Student's one-tailed *t*-test with probability values less than 0.01 being considered significant.

RESULTS

Effect of Interferons on Expression of HLA-DR Antigens by Dispersed Epidermal Cells

To determine their effects on surface HLA-DR expression, *E. coli*-derived IFN-alpha$_2$ and IFN-gamma were tested initially on cultured neonatal human epidermal cells. LCs constitute 2–5% of human epidermal cells [30] and, within the epidermis, may be specifically identified by the presence of cell surface T6 antigen [25]. We [26] and others [27,28] have reported that only half of T6-positive LCs also express HLA-DR antigens. As shown in Table I, the addition of IFN-gamma to human epidermal cell cultures increased the number of $DR^+/T6^+$ LCs detected, even at the lowest concentration (10 units/ml) tested. The number of DR^+ cells approached, but did not exceed, the constant (2.40×10^4) total number of simultaneously detected T6 antigen-bearing LCs. No enhancement of DR-bearing LCs was detected following the addition of IFN-alpha$_2$, even at 10^6 units/ml.

The IFN-gamma enhancement of DR-bearing LCs was not restricted to neonatal epidermal cells but also occurred when adult epidermal cells were studied. In 3 experiments utilizing adult face skin epidermal cell cultures, incubation with 10^3 units/ml of IFN-gamma was found to double the number of epidermal cells expressing HLA-DR antigens from 1.08% ± 0.20 (SEM) of all epidermal cells in control cultures to 2.00% ± 0.48 after 20 h of incubation with IFN-gamma.

TABLE I. *Expression of Langerhans cell HLA-DR antigens following exposure of dispersed epidermal cells to IFN-alpha$_2$ and IFN-gamma*

Treatment	Units/ml	$DR^+/T6^+$ Langerhans[a] Cells × 10^{-4} (SD)	% $T6^+$ LCs
None		1.23 (0.36)	51.2
IFN-alpha$_2$	10^2	1.02 (0.27)	42.5
	10^4	1.23 (0.27)	51.2
	10^6	1.50 (0.35)	62.5
IFN-gamma	10^1	1.93 (0.25)	80.4[b]
	10^2	1.78 (0.45)	74.1[b]
	10^3	2.09 (0.48)	87.0[b]
	10^4	2.32 (0.58)	96.6[b]

[a] Dispersed human neonatal foreskin epidermal cells (5×10^5) were maintained in vitro in the presence and absence of the indicated concentrations of IFN-alpha$_2$ and IFN-gamma, as described in *Materials and Methods*. No $DR^+/T6^-$ were observed in any of these cultures which contained 2.40 (0.17 SD) × 10^4 $T6^+$ LCs. The data presented are the results of 1 experiment and are representative of 4 separate experiments.

[b] Significantly different ($p < 0.01$) from untreated control.

TABLE II. *Effect of IFN-alpha$_2$ and IFN-gamma on expression of HLA-DR antigens on Langerhans cells in situ*

Treatment[a]	Units/ml	$HLA\text{-}DR^+$ Langerhans[b] Cells per mm^2 (SEM)	% Control
None		267.3 (25.6)	100.0
IFN-alpha$_2$	10^1	241.5 (16.1)	90.3
	10^2	257.6 (19.3)	96.3
	10^3	265.6 (20.9)	99.3
	10^4	209.3 (14.5)	78.3
	10^5	276.9 (22.5)	103.5
IFN-gamma	10^1	309.1 (17.7)	115.6
	10^2	383.2 (29.0)	143.3[c]
	10^3	544.2 (29.0)	203.5[c]
	10^4	520.0 (38.6)	194.5[c]
	10^5	566.7 (40.3)	212.0[c]

[a] Four millimeter-diameter specimens of freshly excised human neonatal foreskin, trimmed of fat and dermis, were maintained in vitro as described in *Materials and Methods*.

[b] Epidermal sheets were stained by indirect immunofluorescence for HLA-DR bearing cells as described in *Materials and Methods*. The number of fluorescing, dendritic cells in 10 fields were counted under epifluorescent microscopy (400×) and a mean and SEM per mm^2 calculated.

[c] Significantly different ($p < 0.01$) from untreated control.

Effect of Interferons on Expression of HLA-DR Antigens on LCs in Situ

To further approximate in vivo conditions and to avoid enzymatic treatments and other physical manipulations required to isolate and disperse epidermal cells for culturing [7], superficial specimens of human foreskin were maintained in culture for 20 h in the absence and presence of various concentrations of IFN-gamma and IFN-alpha$_2$. Following treatment of the specimens with NaBr, the number of DR and T6 antigen-bearing cells per mm^2 in the resultant epidermal sheets was calculated. As shown in Table II, exposure to IFN-gamma (10^1–10^5 units/ml) enhanced the detection of DR antigen-bearing epidermal cells with no increases being detected following the addition of identical concentrations of IFN-alpha$_2$. All DR-bearing cells were dendritic, and T6 antigen-bearing LCs were not increased in number.

We found this in vitro method utilizing intact skin specimens to be a simple and reproducible technique for studying LC surface antigens. As detailed in Table III, a series of 9 such in situ experiments using 20 h of foreskin exposure to 10^3 units/ml IFN-gamma reproducibly increased the density of HLA-DR

TABLE III. *IFN-gamma enhancement of Langerhans cell HLA-DR antigenicity in situ*

Experiment[a]	HLA-DR$^+$ Langerhans cells per mm^2 (SEM)		
	Control	IFN-gamma[b]	% Control
1	313.9 (16.1)	529.6 (25.7)	168.7
2	319.5 (10.0)	496.7 (16.9)	155.4
3	294.6 (26.8)	513.5 (36.5)	174.3
4	322.0 (10.4)	604.5 (35.4)	187.7
5	267.3 (25.6)	544.2 (29.0)	203.5
6	273.7 (15.0)	500.7 (12.1)	182.9
7	314.0 (11.1)	567.3 (14.5)	180.6
8	286.6 (9.7)	518.4 (22.5)	180.8
9	342.9 (12.7)	623.1 (17.2)	181.7
		Mean: 177.9	(4.3)

[a] Nine separate experiments were carried out in which human foreskin specimens were prepared, cultured, and analyzed for epidermal HLA-DR antigenicity as described in *Materials and Methods*, employing 10^3 units/ml IFN-gamma.

[b] Each value listed in this column is significantly different ($p < 0.01$) from its corresponding untreated control value.

antigen-bearing LCs over control specimens by 77.9% ± 4.3 (SEM). Extending the duration of incubation with IFN-gamma to 48 h did not result in any further increases in HLA-DR$^+$ LCs.

As observed with dispersed epidermal cell cultures, IFN-gamma also enhanced the expression of HLA-DR by LCs in situ in adult skin specimens. In 2 separate experiments using specimens of adult face skin, incubation with 10^3 units IFN-gamma increased the number of in situ DR$^+$ cells/mm^2 by an average of 80% over controls.

Inhibition of IFN-gamma Enhancement of LC HLA-DR Expression by Monoclonal Anti-IFN-gamma

To be certain that cloned IFN-gamma itself and not some other *E. coli*-derived contaminant possibly present in our IFN-gamma preparation was inducing HLA-DR expression, we studied IFN-gamma induced DR enhancement in the presence of a monoclonal anti-IFN-gamma. The addition of 100 units/ml IFN-gamma to intact foreskin specimens significantly ($p < 0.01$) increased the percentage of HLA-DR$^+$ cells (136.1% ± 3.5) over that present in untreated controls (100.0% ± 2.1). The simultaneous addition of 400 neutralizing units/ml of anti IFN-gamma monoclonal antibody significantly ($p < 0.01$) prevented (102.2% ± 2.2) HLA-DR expression induced by IFN-gamma. The percentage of HLA-DR$^+$ cells in specimens treated with this antibody alone did not differ significantly from untreated control specimens. The presence of a mouse monoclonal anti-IFN-alpha antibody did not significantly prevent IFN-gamma induced HLA-DR expression nor did it affect the number of HLA-DR$^+$ cells in control specimens.

Inhibition of IFN-gamma Induced HLA-DR Expression on LCs by PGE_2

PGE_1 and PGE_2, both products of fatty acid cyclooxygenase action on arachidonic acid, inhibit lymphokine-induced murine macrophage expression of Ia antigens [18,29]. These findings prompted us to determine whether PGE_2 could inhibit optimal induction by IFN-gamma of HLA-DR expression on LCs contained in cultured foreskin specimens. As shown in Table IV, 10^{-7} M PGE_2 effectively inhibited the HLA-DR expression induced by 10^3 units IFN-gamma/ml, while TXB_2 had no such inhibitory activity. This observation suggests that IFN-gamma may be inducing HLA-DR expression on LCs by inhibiting the synthesis of PGE_2.

Enhancement of LC HLA-DR Antigenicity by Fatty Acid Cyclooxygenase Inhibitors

In order to demonstrate that inhibition of PGE_2 synthesis can result in enhanced expression of HLA-DR antigen on LCs, we investigated whether compounds inhibiting PGE_2 synthesis via inhibition of fatty acid cyclooxygenase could in the absence of exogenously added IFN-gamma increase HLA-DR expression. Foreskin specimens were maintained either in RPMI alone or in RPMI containing IFN-gamma at 10^3 units/ml, in the presence or absence of known inhibitory concentrations of indomethacin, a specific cyclooxygenase inhibitor [31] or benoxaprofen, ETYA, and NDGA, compounds which inhibit both the cyclooxygenase and lipoxygenase metabolism of arachidonic acid [32–34]. As shown in Fig 1, all these inhibitors significantly increased the number of HLA-DR antigen-bearing epidermal LCs, with indomethacin, ETYA, and NDGA approaching values induced by IFN-gamma. Thus, known inhib-

TABLE IV. *Effect of prostaglandin E_2 and thromboxane B_2 on IFN-gamma induced HLA-DR expression on Langerhans cells in situ*

Treatment	HLA-DR$^+$ Langerhans[a] Cells % Control (SEM)
None[b]	100.0 (3.9)
IFN-gamma	162.7 (5.1)
PGE_2	102.8 (4.3)
IFN-Gamma + PGE_2	123.2 (5.1)[c]
None[d]	100.0 (5.9)
IFN-gamma	172.1 (7.6)
TXB_2	101.9 (7.8)
IFN-gamma + TXB_2	157.3 (4.3)[e]

[a] Human foreskin specimens were prepared, cultured, and analyzed for epidermal HLA-DR antigenicity as described in *Materials and Methods* and the number of HLA-DR$^+$ LCs expressed as a percentage of those present in the untreated control.

[b] Results are the mean of 9 separate experiments employing 10^3 units/ml IFN-gamma and 10^{-7} M PGE_2.

[c] Significantly different ($p < 0.01$) from value for IFN-gamma treatment alone.

[d] Results are the mean of 5 separate experiments employing 10^3 units/ml IFN-gamma and 10^{-8} M TXB_2.

[e] Does not significantly differ ($p > 0.01$) from value for IFN-gamma treatment alone.

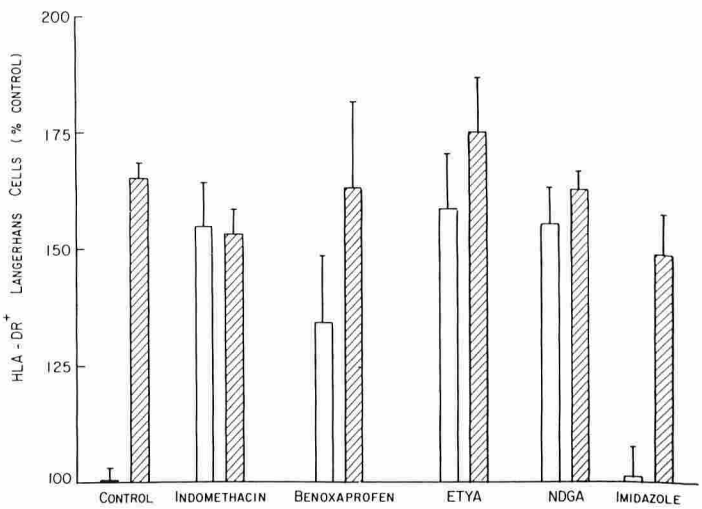

FIG 1. Effect of arachidonate cyclooxygenase inhibitors on the expression of Langerhans cell HLA-DR antigenicity in situ.

Superficial foreskin specimens were prepared and maintained as described in *Materials and Methods* in the absence or presence of the compounds indicated. The *bars* represent the mean ± SEM of 16 separate experiments for controls, 8 experiments for indomethacin (10^{-5} M), 6 experiments for benoxaprofen (10^{-4} M), 3 experiments for ETYA (10^{-5} M), 4 experiments for NDGA (10^{-5} M), and 3 experiments for imidazole (10^{-4} M). *Cross-hatched bars* indicate the presence of 10^3 units/ml IFN-gamma and *open bars* indicate its absence. Results are shown as the number of HLA-DR$^+$ cells expressed as a percentage of those present in untreated controls. All treatments significantly ($p < 0.01$) increased HLA-DR$^+$ cells over untreated controls with the exception of the addition of imidazole alone.

itors of PGE_2 synthesis mimic the action of IFN-gamma inducing HLA-DR antigen expression on LCs, a situation having been previously reported for murine macrophages [29]. Incubation in the presence of imidazole, a relatively selective inhibitor of thromboxane synthetase, failed to induce HLA-DR expression [35].

DISCUSSION

We have studied the effects of cloned IFN-gamma and IFN-alpha$_2$ upon the expression of HLA-DR histocompatibility antigens by human epidermal cells maintained in vitro as suspension cultures and as intact skin explants. The data presented show that cloned human IFN-gamma, but not IFN-alpha$_2$, increases the number of epidermal cells expressing HLA-DR antigens approximately 2-fold after 20 h of exposure. HLA-DR was induced only on LCs as only T6-positive cells expressed HLA-DR antigen, and the total number of DR-positive cells (constitutive + induced) never exceeded the number of T6-positive LCs present. Whether IFN-gamma, in addition to inducing the presence of HLA-DR determinants on $DR^-/T6^+$ LCs, can also increase the degree of expression of HLA-DR on $DR^+/T6^+$, as has been reported for human monocytes [20], cannot be determined by simple immunofluorescent microscopy. However, the induction of HLA-DR antigens by IFN-gamma (and not by IFN-alpha$_2$) on $DR^-/T6^+$ LCs is consistent with similar inductions reported on other macrophage and macrophage-like cells otherwise expressing low or undetectable levels of DR-antigens [15–18,22]. Although recent reports indicate that IFN-gamma may also induce HLA-DR expression on epidermal keratinocytes, such induction reportedly required 4–8 days' incubation and was never observed to occur in our short-term (20 h) cultures [36].

The intracellular mechanisms responsible for IFN-gamma induction of LC HLA-DR expression have also been investigated and our results suggest that IFN-gamma may act by inhibiting the synthesis of PGE_2. This conclusion was based on our observations that (1) PGE_2 inhibited IFN-gamma induction of HLA-DR, and (2) compounds inhibiting PGE_2 production via blockade of fatty acid cyclooxygenase can increase HLA-DR expression on LCs in the absence of IFN-gamma. These results are again consistent with previous results concerning Ia induction in murine macrophages [18,29]. The actions of IFN-gamma and fatty acid cyclooxygenase inhibitors were not additive, but at the concentrations tested each agent alone induced the numbers of HLA-DR bearing LCs to approach the total number of T6-positive LCs. At lower concentrations such additive effects, if present, may be detected.

The question of whether IFN-gamma acts directly on LCs to inhibit PGE_2 production or indirectly via inhibiting PGE_2 production by other epidermal cells such as keratinocytes has not been addressed in this study. However, preliminary results using T6-positive LCs isolated by panning techniques [37] indicate IFN-gamma acts directly on LCs to increase HLA-DR expression. Such a direct mechanism of action would be consistent with recent reports indicating IFN-alpha and IFN-beta act directly on macrophages and monocytes to inhibit prostaglandin synthesis by blocking phospholipase activation [38, 39]. However, additional experiments are required to determine the exact role of arachidonate metabolites in constitutive and IFN-gamma induced HLA-DR expression by epidermal LCs.

Epidermal LCs function as stimulator cells of allogeneic T-cell activation and as antigen-presenting cells in antigen-induced T-cell proliferation and in cytotoxic T-lymphocyte generation [10–13,24]. These immune functions are genetically restricted, being regulated by HLA-DR, or their murine equivalent, Ia, antigens. The enhancement of epidermal LC DR-antigenicity following exposure to IFN-gamma (although not to IFN-alpha$_2$) may imply concomitant enhancement of DR-regulated LC functioning, as this has been reported in the case of lymphokine-induced expression of Ia determinants by murine macrophage tumor cell lines [40,41]. LC accessory cell functions are in all likelihood active in contact hypersensitivity, skin graft rejection and certain types of drug hypersensitivities. We are presently examining whether the induction of HLA-DR antigens on LCs by IFN-gamma results in an increase in LC accessory/stimulatory cell functions.

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