Journal of Clinical Immunology, Vol. 6, No. 2, 1986

Defective Gamma-Interferon Production in Peripheral Blood Leukocytes of Patients with Acute Tuberculosis

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Accepted: October 10, 1985

Production of interferon (IFN)-gamma by peripheral blood leukocytes (PBL) was examined in cultures of unseparated fresh whole blood exposed to phytohemagglutinin (PHA), concanavalin A (Con A), or pokeweed mitogen (PWM). The yield of IFN-gamma was measured by a newly developed immunoradiometric assay. Nine of 14 patients with acute pulmonary tuberculosis (TB) showed a depressed IFN-gamma response to Con A and/or PWM. Only four of these TB patients also showed a depressed IFN-gamma response to PHA. Stimulation of the patients' PBL cultures with PHA in the presence of exogenous interleukin 2 (IL 2) produced normal IFN-gamma yields in all but the most severely depressed patients. PBL cultures of TB patients with defective IFN-gamma production in response to mitogenic lectins also produced less IFN-gamma after stimulation with tuberculin PPD. Although some patients showed a moderate degree of lymphopenia, their OKT4/T8 lymphocyte ratios were mostly normal or close to normal, with the notable exception of one TB patient who has been diagnosed to have the acquired immune deficiency syndrome (AIDS).

KEY WORDS: Interleukin 2; T-cell mitogens; tuberculin; helper/suppressor T cells; acquired immune deficiency syndrome (AIDS).

INTRODUCTION

Interferon (IFN)-gamma plays an important role in the modulation of several events during the generation of immune responses, including the activation of macrophages for microbicidal (1) and tumoricidal (2, 3) activities; the induction of MHC antigens, especially the class II MHC antigens including Ia antigen (4); the induction of Fc receptor expression (5, 6); and the stimulation of B-cell differentiation (7). These and other immunomodulatory actions of IFN-gamma (reviewed in Refs. 8 and 9) may be impaired during primary or acquired immunological disorders. One reason for such an impairment can be a decreased production of IFN-gamma as a consequence of a defect in the cell populations producing it or some other functional abnormality.

Evaluation of interferon (IFN)-gamma production in peripheral blood leukocytes (PBL) from patients with immune disorders and/or infectious diseases may help to clarify the pathophysiological mechanisms involved in the disease process. In this study, we have examined IFN-gamma production in PBL cultures from patients with acute pulmonary tuberculosis (TB). We have employed a simple method of evaluation of IFN-gamma production in cultures of the patients' unseparated whole blood. IFN-gamma yield from the cultures was measured with the aid of a recently developed sandwich immunoradiometric assay (10) affording greater sensitivity, accuracy, and specificity than conventional bioassays. About two-thirds of the TB patients examined showed a marked decrease in IFN-gamma production in response to at least one of the lectins employed. The addition of interleukin 2 (IL 2) to the cultures largely restored defective IFN-gamma production in a majority of the patients. The functional consequences of defective IFN-gamma production in patients with severe acute pulmonary TB remain to be determined.

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0271-9142/86/0300-0146$05.00/0

MATERIALS AND METHODS

Subjects. Fourteen patients hospitalized with the diagnosis of acute pulmonary TB were studied. The presumptive diagnosis of TB was based on the demonstration of acid-fast bacilli in the sputum and/or caseating granulomata on tissue biopsy and was subsequently confirmed by a positive culture for *Mycobacterium tuberculosis*. The disease stage ranged from pleural effusion with no other pulmonary involvement ("effusion"), to pulmonary involvement without evidence of cavitation ("moderate"), to evidence of cavitation ("advanced"). Extrapulmonary involvement, if any, was confirmed by lymph node biopsy. Blood for the determination of IFN-gamma production was taken before the initiation of antibiotic therapy, except in patient 1, whose blood was drawn 4 days after the initiation of therapy, and patients 7 and 8, who had been treated for 34 and 44 days, respectively, at the time their blood was first examined for IFN-gamma production but were not responding to therapy (see Table II). In some patients another determination of IFN-gamma production was made after the onset of therapy.

Twenty-one healthy hospital employees served as control subjects for the determination of the normal ranges of IFN-gamma production in response to mitogenic lectins.

Mitogens. Phytohemagglutinin (PHA) was prepared in the laboratory of Dr. Joel D. Oppenheim at NYU Medical Center. Concanavalin A (Con A) was purchased from Pharmacia, Piscataway, NJ, and purified pokeweed mitogen (PWM) from E.-Y. Laboratories, San Mateo, CA. Unless indicated otherwise, PHA was added to cultures of peripheral blood leukocytes (PBL) at a final concentration of 2 μg/ml, Con A at 5 μg/ml, and PWM at 1 μg/ml. Preservative-free tuberculin PPD was from Connaught Laboratories, Willowdale, Ontario, Canada; a concentration of 5 μg/ml was used for the stimulation of PBL cultures.

Interleukin 2. Recombinant human IL 2, kindly provided by Dr. Richard J. Robb, was produced in *Escherichia coli* and purified by reverse-phase liquid chromatography on a Beckman RPSC column to a purity of >98% as judged by sodium dodecyl sulfate–polyacrylamide gel electrophoresis. Stock solutions contained between 75,000 and 200,000 IL 2 units/ml and the level of endotoxin contamination was approximately 0.5 pg/1000 IL 2 units. The potency of IL 2 is expressed in terms of reference units of bioactivity, based on the NIH reference reagent supplied by the Biological Response Modifiers Program of the National Cancer Institute. IL 2 activity was quantitated by the stimulation of [^{3}H]thymidine incorporation in a murine cytotoxic T-lymphocyte line (CTLL-2) kindly provided by Dr. Karl Welte of the Sloan–Kettering Institute (11).

Stimulation of IFN-Gamma Production in Cultures of Peripheral Blood Cells. Cultures of unseparated human blood were prepared according to a simple method similar to that employed by Kirchner *et al.* (12). Fresh unseparated blood, anticoagulated with sodium heparin (15 USP units/ml), was diluted with 9 vol of serum-free RPMI 1640 medium, supplemented with Hepes (6 m*M*), Tricine (3 m*M*), gentamicin (50 μg/ml), and glutamine (2 m*M*). The cell suspension was then distributed in 17 × 100-mm plastic tissue culture tubes (1 ml/tube) and mitogen, PPD, or IL 2 was added as indicated. The tubes were loosely capped and incubated at 37°C in a CO_2 incubator. At the end of incubation supernatants from the cultures were harvested and the IFN-gamma present was quantitated in an immunoradiometric assay as described below. All IFN-gamma assays were done in duplicate.

Radioimmune Assay (RIA) of IFN-Gamma. A recently developed solid-phase sandwich RIA (10), employing two murine monoclonal antibodies, has been used for the quantitation of IFN-gamma. RIA kits (IMRX IFN-gamma RIA), containing antibody-coated polystyrene beads and a ^{125}I-labeled solution of tracer antibody, have been manufactured and supplied by Centocor, Malvern, PA. This assay is specific (unlike most bioassays, the RIA does not detect IFN-alpha or IFN-beta) and sensitive (the lower limit of sensitivity is 0.1–0.2 unit/ml). IFN-gamma titers are expressed in reference units based on the value of NIH standard Gg 023-901-530 (National Institute of Allergy and Infectious Diseases, Bethesda, MD).

RESULTS

IFN-Gamma Production in Response to PHA, Con A, and PWM in PBL Cultures from Healthy Donors. The availability of a sensitive and specific immunoradiometric assay for IFN-gamma (10) enabled us to develop a standardized procedure for the evaluation of IFN-gamma production in PBL cultures stimulated with mitogenic lectins or anti-

Table I. Summary of IFN-Gamma Production in Cultures of Unseparated Blood from 21 Normal Individuals

Mitogen[a]	IFN-gamma ref. units/ml produced[b]	
	Mean ± SD	Range
None	0.66 ± 0.43	0.18–1.86
PHA (2 μg/ml)	41.98 ± 22.25	5.58–92.46
PHA (10 μg/ml)	40.18 ± 19.02	7.79–82.21
Con A (5 μg/ml)	37.44 ± 24.43	6.25–85.64
PWM (1 μg/ml)	43.28 ± 25.40	7.39–89.62

[a]Heparinized blood was diluted 1:10 in serum-free RPMI 1640 medium containing the appropriate mitogen at the indicated concentration and incubated in loosely capped 17 × 100-mm plastic tissue culture tubes (1 ml/tube) at 37°C in a CO_2 incubator.
[b]Based on triplicate determinations by RIA in culture supernatants collected after 24 hr of incubation.

gens. Our aim was to use a method that would be accurate and reproducible while requiring as little manipulation of human blood specimens as possible. After some preliminary experiments we adopted a method similar to that described by Kirchner *et al.* (12), which employs cultures of unseparated fresh human blood exposed to a mitogen or antigen as described in Materials and Methods.

PHA (2 and 10 μg/ml), Con A (5 μg/ml), and PWM (1 μg/ml) were chosen after preliminary experiments to evaluate the response of PBL cultures of 21 healthy volunteers (Table I). These data established the "normal range" of IFN-gamma yields for each of the lectins under the experimental conditions employed.

IFN-Gamma Production in PBL Cultures from TB Patients. Fourteen TB patients were included in the study (Table II). Hematologic examination revealed leukocytosis in three, severe leukopenia in one, and lymphopenia in three patients. The number of total T cells ($OKT3^+$) was slightly to moderately decreased in three patients. Only one patient (No. 13) showed a severely decreased T helper/T suppressor-cell ratio; this patient was diagnosed as having acquired immune deficiency syndrome (AIDS) and Kaposi's sarcoma along with TB.

IFN-gamma production was evaluated in cultures of unseparated fresh blood from these patients using the same mitogenic lectins as for the healthy volunteers (Table III). In addition, IFN-gamma production was also measured in cultures incubated with a high dose of exogenous recombinant IL 2 or a mixture of IL 2 and PHA, as well as with PPD (13). Nine of the 14 TB patients showed some decrease in the yields of IFN-gamma. Of these, five showed depressed IFN-gamma production with Con A and/or PWM but not with PHA. Another four patients showed decreased IFN-gamma yields with all three lectins and the same patients also produced low yields in response to IL 2. However, only in one patient (No. 14) did combined stimulation with PHA and exogenous IL 2 fail to correct the deficiency seen in cultures stimulated with PHA alone.

IFN-gamma production in response to tuberculin PPD was examined in 11 of the 14 patients. Patient 13 (who was diagnosed as having AIDS with Kaposi's sarcoma and TB) failed to produce IFN-gamma. All other patients who showed defective IFN-gamma production with mitogens produced low yields with PPD (<25 units/ml). The highest levels of IFN-gamma (>140 units/ml) were produced by patients 4 and 5, who also showed normal levels of IFN-gamma production with the mitogenic lectins. On the other hand, patient 1, who responded normally to all mitogenic lectins, did have a very low response to PPD. Since we have not yet established the range of IFN-gamma yields in response to PPD in healthy PPD skin-test positive donors, we do not know what can be considered a "normal" response range under the experimental conditions employed.

Based on the patterns of response to mitogenic lectins, three degrees of defective IFN-gamma production can be distinguished, designated + to +++, as explained in Table III, footnote *b*. However, attempts to correlate the degree of defective IFN-gamma production in response to mitogenic lectins with the severity of disease or hematologic findings (Table II) were only partly successful. The patient showing the greatest defect in IFN-gamma production (No. 14) had been hospitalized for over 5 months, his culture yielded *M. tuberculosis* resistant to isoniazid, rifampin, streptomycin, and ethambutol, and he was not responding to therapy. The patient had leukocytosis with lymphopenia but since he was cachectic it was not possible to obtain enough blood for a determination of the $OKT3^+$-cell count and of the T4/T8 ratio. Patient 13, diagnosed as having AIDS with TB and Kaposi's sarcoma, was leukopenic and lymphopenic and he had <2% $OKT4^+$ along with 67% $OKT8^+$ cells (T4/T8 ratio, <0.1). In most other patients the clinical condition and hematologic findings showed no clear correlation with defective IFN-gamma production.

Table II. Review of Clinical and Laboratory Findings of TB Patients Included in the Study

Patient no.	Age and sex	Clinical condition and degree of pulmonary involvement	Other conditions[a]	Total WBC/mm^3 × 10^{-3} (3.6–10.0)[b]	Total lymphocytes/mm^3 (1029–3341)[b]	%OKT3$^+$ (60–80)[b]	T4/T8 ratio (1.4–2.6)[b]	Defective IFN-gamma production[c]
1	62, M	Advanced	Cor pulmonale	6.0	1680	51	2.6	−
2	43, M	Moderate to advanced	—	7.0	2800	77	0.9	−
3	34, M	Moderate + effusion	iv drug use	6.2	3100	75	1.2	−
4	25, F	Moderate to advanced	iv drug use	6.7	1407	ND	ND	−
5	29, F	Effusion	—	10.6	848	ND	ND	−
6	31, M	Moderate + extrapulmonary	—	5.7	1140	72	1.8	+
7	57, M	Advanced (antibiotic resistant)	Alcoholism	8.3	2158	40	2.3	+
8	37, M	Advanced (antibiotic resistant)	Alcoholism	16.5	2145	51	2.7	+
9	49, M	Moderate + effusion	Chronic glomerulonephritis, alcoholism	4.9	1176	ND	ND	+
10	29, M	Effusion	Alcoholism	5.4	1080	69	3.7	+
11	35, M	Moderate	—	5.9	1770	59	0.9	++
12	46, M	Advanced	iv drug use	9.1	3822	ND	ND	++[d]
13	58, M	Moderate	AIDS (Kaposi's sarcoma), anergy	1.9	855	69	<0.1	++
14	47, M	Advanced (antibiotic resistant)	Alcoholism, severe hypoalbuminemia	17.1	684	ND	ND	+++

[a]All patients (with the exception of No. 6) had hypoalbuminemia.
[b]Numbers in parentheses indicate ranges of normal values.
[c]See Table III for specific data and explanation.
[d]Data on response to PHA in the presence of IL 2 not available for this patient.

DISCUSSION

We have shown that about two-thirds of patients with acute pulmonary TB had a demonstrable decrease in IFN-gamma production by their PBL after stimulation with mitogenic lectins. Preliminary evidence suggests that as patients respond to antibiotic therapy, the capacity of their PBL to produce IFN-gamma improves (results not shown). Deficient IFN-gamma production in TB patients is reminiscent of a similar impairment in IFN-gamma production demonstrated in patients with lepromatous leprosy (14). More work is needed to determine whether proliferative responses to mitogens or PPD are also impaired in TB patients with decreased IFN-gamma production.

Most TB patients included in our study were not severely lymphopenic. With the exception of one patient (No. 13), whose TB turned out to represent an opportunistic infection due to AIDS, the TB patients did not show gross abnormalities in the number of T cells or ratio of helper/suppressor T cells. Defective IFN-gamma production in TB patients might be related to increased suppressor cell activity. It is known that suppressor T cells may play a central role in limiting cellular responses to various mycobacterial antigens in experimental animals or patients infected with mycobacteria (15, 16). In addition, adherent monocytes/macrophages also may mediate suppression in mycobacterial infections (17, 18). This suppression of cellular immune responses is specific in its induction but it can result in reduced responsiveness to unrelated antigens or mitogens (15).

Several groups reported a decreased capacity of lymphocytes to produce IFN-gamma in AIDS patients (19–21). We also examined IFN-gamma production in response to T-cell mitogens in PBL from a group of AIDS patients by the same procedure as used here for the TB patients (results not shown). Most of the AIDS patients examined had Kaposi's sarcoma but no opportunistic infections at the time of examination. Only about one-third of these AIDS patients showed a clearly decreased production of IFN-gamma, despite the fact that most of them were severely lymphopenic and had a marked diminution in OKT4/T8 ratios. These results agree with those of Murray *et al.* (20), who reported that in many AIDS patients IFN-gamma production on stimulation with Con A was normal despite a drastic decrease in T-helper cells and that impairment in IFN-gamma production in these patients was more

Table III. IFN-Gamma Production in Cultures of Unseparated Blood from TB Patients

Patient no.	IFN-gamma ref. units/ml produced in response to[a]							Defective IFN-gamma production[b]
	No mitogen	PHA	Con A	PWM	IL 2	PHA + IL 2	PPD	
1	1.3	44.3	14.1	18.7	40.6	62.0	4.0	–
2 (12/18/84)	1.4	63.1	12.2	38.9	38.7	75.0	38.6	–
(1/14/85)	0.4	63.5	10.1	ND[c]	ND	ND	54.4	–
3	0.6	75.4	24.9	20.9	28.9	101.8	ND	–
4	0.8	40.6	12.5	25.6	38.4	84.6	148.2	–
5	0.4	91.3	6.3	16.1	ND	ND	168.7	–
6	0.2	58.1	10.8	*6.5*[d]	6.6	68.9	20.9	+
7	0.4	24.3	*3.2*	*3.4*	ND	ND	ND	+
8 (8/8/84)	0.4	12.4	*2.5*	*3.9*	ND	ND	ND	+
(10/3/84)	1.9	24.0	7.1	*4.1*	ND	ND	ND	+
9 (12/27/84)	0.8	26.5	*5.5*	12.5	18.2	35.3	15.7	+
(1/14/85)	0.4	12.6	*1.6*	ND	ND	ND	11.0	+
10	0.5	13.9	*2.3*	*2.1*	ND	ND	2.8	+
11	0.2	*5.5*	*0.9*	*1.4*	*1.8*[e]	28.7	2.0	++
12	0.7	*3.2*	*1.2*	*4.5*	ND	ND	5.3	++
13	0.5	*5.4*	*1.6*	*0.7*	*0.4*	41.2	0.2	++
14 (8/8/84)	0.5	*4.9*	*1.0*	*2.2*	ND	ND	ND	
(1/14/85)	0.4	*3.4*	*0.5*	*0.8*	*0.4*	*5.3*	4.8	+++

[a]Stimulation of IFN-gamma production was as described in Table I, except that PHA was used at 2 μg/ml only and IL 2 was added at 2500 units/ml. Supernatants from cultures stimulated with PPD (5 μg/ml) were collected at 72 hr after stimulation. All other cultures were harvested at 24 hr.

[b]–, responses to PHA, Con A, and PWM above low-normal level in all groups; +, decreased production in response to Con A and/or PWM; ++, decreased response to Con A, PWM, and PHA; +++, decreased response to all mitogens and to PHA in the presence of IL 2. (Results obtained with PPD are not included in this summary.)

[c]Not done.

[d]Italicized values indicate IFN-gamma yields below the lowest value of normal controls.

[e]Although the range of normal IFN-gamma yields produced in response to exogenous IL 2 has not been established, values below 5 units/ml have been arbitrarily designated as depressed.

pronounced in response to specific antigens. Thus, production of IFN-gamma in response to the common T-cell mitogens actually appears to be more impaired in TB patients than in AIDS patients. These findings support the notion that impaired IFN-gamma production in TB patients is likely to be a specific lesion and not merely secondary to other factors, e.g., alcoholism, hypoalbuminemia, etc.

IL 2 is known to exert a positive regulatory influence on IFN-gamma production in the normal host. The addition of IL 2 to PBL cultures was shown to be synergistic with mitogenic lectins in IFN-gamma induction (22, 23), and at high concentrations, IL 2 alone induced substantial levels of IFN-gamma (13, 22–25). Our data show that in the presence of PHA exogenous IL 2 could restore deficient IFN-gamma production in PBL from most TB patients. These results are in agreement with earlier reports showing that exogenous IL 2 restored the ability to release IFN-gamma (19) along with impaired proliferative responses (26, 27) in AIDS patients' lymphocytes. Similar findings were reported in patients with lepromatous leprosy (14, 28). Taken together these results suggest that the impairment in IFN-gamma production in some instances might be secondary to a defect in IL 2 generation. Preliminary data support the idea that impaired IFN-gamma production in TB patients is accompanied by lowered IL 2 production (not shown).

Our preliminary results suggest that IFN-gamma induction with PPD is also depressed in TB patients. Onwubalili *et al.* (29) have recently shown that of a group of 25 TB patients, 9 produced low levels of IFN-gamma in response to PPD. Responses to other recall antigens have not yet been examined. It is well known that T cells and their products enhance the microbicidal activity of macrophages against mycobacteria (18, 30) and IFN-gamma is likely to be the major T-cell product responsible for this action (1). Consequently, a defect in IFN-gamma production in the intact organism might contribute to the impaired host defenses against *M. tuberulosis*.

ACKNOWLEDGMENTS

We thank Dr. Richard J. Robb for the gift of interleukin 2, and Michele C. Maniscalco and Karen Shipp for editorial assistance and typing.

This study was supported in part by NIH Research Grants AI-07057 and AI-12948 and by a grant from Centocor, Inc.

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