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RECOMBINANT γ INTERFERON INDUCES HYPERTRIGLYCERIDEMIA AND INHIBITS POST-HEPARIN LIPASE ACTIVITY IN CANCER PATIENTS

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Several common clinical and biochemical abnormalities characterize mammalian hosts with chronic illness caused by infection or malignant disease. These abnormalities include fever, a catabolic state resulting in a severe wasting diathesis, and increased specific serum proteins referred to as acute-phase proteins (1, 2). In addition to the above derangements, many reports have described a marked hypertriglyceridemia, which occurs in animals in response to tumors (3, 4), endotoxemia (5–8), and bacterial (9, 10), viral (11), and protozoal infections (12). Several investigators have demonstrated that in these animals, development of hypertriglyceridemia is associated with elevation of very low-density lipoproteins (VLDL)[1] (3, 4, 12). The high levels of this lipoprotein result from a clearing defect caused by suppression of the key enzyme of plasma triglyceride metabolism (13), lipoprotein lipase (LPL) (5, 6, 7, 10, 12). In vitro and in vivo studies (14–17) have revealed that this suppression of LPL activity can be mediated by cachetin and/or IL-1, both of which are factors produced by activated macrophages. Interestingly, the *N*-terminal sequence of cachectin has recently (18) been discovered to be strongly homologous to tumor necrosis factor (TNF), and purified cachectin possesses TNF cytolytic activity, indicating that cachectin and TNF are identical. In addition, one or more mediators released by activated macrophages in vitro have been shown (19) to regulate other key lipogenic processes, i.e., by suppressing enzymes important in de novo fatty acid biosynthesis, such as acetyl–coenzyme A carboxylase and fatty acid synthetase. These

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[1] *Abbreviations used in this paper:* LPL, lipoprotein lipase; TNF, tumor necrosis factor; VLDL, very low-density lipoprotein.

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data suggest that reticuloendothelial cells may provide a communication link between the body's immunoregulatory and energy storage systems.

IFN-γ is a lymphokine derived primarily from T cells, which has important antiviral, antimicrobial, and antiproliferative properties (20). In addition, it is a potent immunoregulator, particularly of macrophage activity (21). However, interaction between this molecule and lipid metabolic pathways has not been previously described. We report that cancer patients treated with rIFN-γ develop consistent derangements in lipid metabolism. These derangements bear a strong resemblance to the hypertriglyceridemic state, described in animals in response to invasive stimuli, and attributed to monokine induction.

Materials and Methods

Interferon. The rIFN-γ used in this investigation is identical in sequence to native human IFN-γ, except for the presence of a methionine residue at the *N*-terminal (22). This material was produced in *Escherichia coli*, using recombinant DNA technology (23, 24). The final product is >98% pure, as determined by SDS-PAGE, and contains <0.5 ng endotoxin per milligram of protein by the limulus amoebocyte lysate assay (data on file; Genentech Inc.). The specific activity of rIFN-γ is ~2×10^7 U/mg protein, based on antiviral activity assessed by inhibition of encephalomyocarditis virus replication in A549 cells (human lung carcinoma cell line), corrected to the reference IFN-γ standard Gg 23-901-530 of the National Institutes of Health, Bethesda, MD.

Study Design. Patients with histologic proof of malignancy were entered on phase I and II studies of rIFN-γ (25). In the phase I study, a minimum of two patients were entered sequentially at each of the following dose levels: 0.01, 0.05, 0.10, 0.25, 0.50, and 1.0 mg/m^2/d of rIFN-γ, i.m. In the phase II study, patients received i.m. rIFN-γ at a dose of 0.25 mg/m^2/d for the first week and 0.5 mg/m^2/d thereafter. The duration of treatment was 42 d. Informed consent was obtained from each patient.

Blood samples for triglyceride and cholesterol levels were drawn on day 0 and then weekly during the study period. All patients had fasted for 12 h before having their blood drawn. After we stopped rIFN-γ therapy, we continued to monitor blood lipid levels weekly until they returned to baseline values. Our preliminary observations of increasing triglyceride levels in several patients prompted the addition of blood tests for lipoprotein electrophoresis, post-heparin lipase activity, and serum TNF titers.

Lipoprotein Electrophoresis. Blood was obtained for lipoprotein electrophoresis on days 0 and 14, after a 12-h fast. Lipoproteins were resolved from serum by agarose gel electrophoresis. The gels were stained with Sudan Red dye.

Lipase Activity after Heparin Injection. On days 0 and 14, patients received an i.v. injection of 100 U/kg of heparin. 20 min later, 10 ml of blood was drawn and immediately placed on ice. Post-heparin lipase levels were measured after separation of total lipase by affinity chromatography. 0.5 ml of plasma was incubated in the cold with 0.5 ml of heparin-Sepharose and 0.5 ml of 0.3 M NaCl, buffered to pH 7.4 with 5 mM barbital. After washing the heparin-Sepharose with 2.0 ml of the same 0.3 M NaCl buffer, total lipase was eluted with the same buffer containing heparin at 10 g/liter (26). The enzymatic assay was performed using the method of Voyta et al. (27). Triplicate determinations were made for each blood sample.

Assay for Inhibition of Lipase Enzymatic Activity In Vitro. To determine whether rIFN-γ is able to directly inhibit lipase enzymatic activity, the following experiment was performed. Post-heparin plasma from a normal healthy donor was subjected to affinity chromatography on heparin-Sepharose, as described above. The fraction containing the enzymatic activity was then aliquoted into tubes containing serial dilutions ranging from 0.003 to 300 μg/ml of rIFN-γ, as well as a control tube with buffer only. After a 30-min preincubation, the lipase/rIFN-γ mixtures and the control were used in the standard lipase assay, in triplicate. Similar experiments were also performed using highly purified LPL isolated from cow's milk (28).

TNF Assays. Blood was obtained for serum TNF assays at three time points, i.e., before and 4 h after the first injection of rIFN-γ, and during the second week of therapy. Blood samples were centrifuged, and the serum was decanted and stored at 0°C until analysis. Serum TNF titers were measured by an ELISA at Genentech, Inc. A solid-phase ELISA was performed using a sandwich technique with two polyclonal antibodies to TNF, one of which was conjugated to a horseradish peroxidase label. The lower limit of sensitivity of the assay is 50 pg/ml.

Results

Patient Characteristics. Triglyceride and cholesterol values were evaluated for 30 patients treated sequentially on our phase I and II studies who received i.m. rIFN-γ for 14 consecutive days without dose reductions. 16 male and 14 female patients participated in the study, and they ranged in age from 23 to 70 yr old (median age, 45 yr). Performance status, according to the Karnofsky criteria (29), was excellent (median, 80%; range, 75–100%). At the start of the study, patients' weights were 85–210% (median, 112%) of ideal body weight (30). 21 patients had solid tumors: 6 with renal cell carcinoma, 5 melanoma, 4 colon carcinoma, 3 sarcoma, 2 cases of breast cancer, and 1 patient with lung adenocarcinoma. Nine patients had hematological malignancies, including five with chronic lymphocytic leukemia, two with chronic myelogenous leukemia, and two with lymphoma.

Side Effects. Fever, chills, and fatigue were the most common side effects of rIFN-γ therapy, and were encountered in virtually all patients (31). At doses ≤ 0.5 mg/m^2/d, these symptoms were tolerated with minimal change in performance status, and they tended to diminish after the initial 4–5 d of therapy. Patients were instructed to follow their normal dietary habits during the study and were encouraged to drink fluids. Nevertheless, weight loss occurred in most patients. The median weight lost after 2 wk of therapy was 0.5 kg; after 6 wk, 1.5 kg. Mild nausea and anorexia occurred in about one-third of patients during the initial week of therapy. Vomiting did not occur. Since daily caloric counts were not assessed, it is not clear whether these symptoms accounted for the weight loss. Mild hepatic dysfunction (elevation in liver enzymes to two to three times baseline levels) occurred in 11 of 30 patients; mild proteinuria (1+ by urine dipstick), in 2 of 30 patients. No other significant changes in renal function, as measured by blood urea nitrogen and serum creatinine, were observed.

Blood Lipid Levels. Hypertriglyceridemia was one of the most common effects observed after rIFN-γ therapy. 23 of 30 (77%) patients showed a >25% increase in triglyceride levels on day 14 with respect to baseline levels (Fig. 1). The increase usually occurred by day 7 of therapy, peaked between the second and third week, and then remained stable. In general, triglyceride values returned to baseline levels within 2–3 wk after discontinuation of rIFN-γ injections. Elevation of triglyceride levels appeared to be dose-related. Only 1 of 7 (14%) patients treated with a dose <0.25 mg/m^2/d, vs. 22 of 23 (96%) patients treated with ≥ 0.25 mg/m^2/d of rIFN-γ showed an increase in triglyceride values ($p < 0.001$, Fisher's exact test). However, increasing the dose above 0.25 mg/m^2/d did not result in an increase in the magnitude of triglyceride elevation; the mean increases in triglyceride values at doses of 0.25, 0.5, and 1.0 mg/m^2/d were 170, 217, and 140 mg/dl, respectively. The mean ±SD of the day 0 triglyceride levels

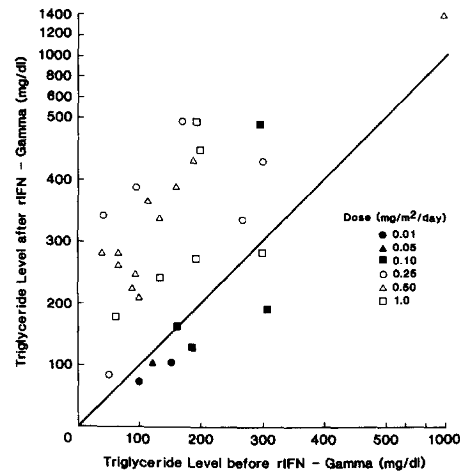

FIGURE 1. Comparison of triglyceride levels before injection and on day 14 of i.m. administration of rIFN-γ.

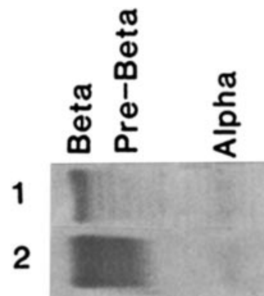

FIGURE 2. Comparison of lipoprotein electrophoresis pattern of patient 5 (Table I) on day 0 (lane 1) and day 14 (lane 2) of i.m. administration of rIFN-γ.

for the 23 patients treated with ≥0.25 mg/m^2/d of rIFN-γ was 180 ± 190 mg/dl, vs. a level of 370 ± 242 mg/dl on day 14 (p <0.001, paired t test). Changes in triglyceride level did not correlate with rIFN-γ-induced changes in hepatic or renal function. Changes in cholesterol levels were not statistically significant.

Lipoprotein Electrophoresis. To characterize this hyperlipidemia, we also performed lipoprotein electrophoresis on 12 patients, before, and 14d after they received ≥0.25 mg/m^2/d of rIFN-γ. Representative data are shown in Fig. 2. On day 0, 2 of 12 (17%) patients had a type 4 hyperlipoproteinemia pattern, while the other 10 patients had a normal lipoprotein profile. On day 14, 11 of 12 (92%) patients manifested a type 4 hyperlipoproteinemia profile. A type 4 profile was defined by the presence of high triglyceride levels, absence of a cream-like layer of chylomicrons on visual inspection of the serum, and an increased pre-β fraction (VLDLs) on lipoprotein electrophoresis.

Post-heparin Lipase Activity. Mechanisms that could account for increased triglyceride values with high VLDLs include enhanced synthesis or decreased clearance. Triglyceride clearance from the circulation is dependent on the action of the enzyme, LPL (32). This enzyme (as well as hepatic lipase) is released into the plasma after the administration of heparin. Therefore, post-heparin lipase

TABLE I
Effect of rIFN-γ on Patient Lipid Profiles

Patient	Post-heparin lipase activity*		Triglyceride		Cholesterol		Lipoprotein phenotype[§]	
	Day 0	Day 14	Day 0	Day 14	Day 0	Day 14	Day 0	Day 14
	μmol/ml/h		*mg/dl*		*mg/dl*			
1	2.13 ± .05	0.05 ± .066	37	344	200	203	Normal	Type 4
2	3.52 ± .25	2.74 ± .35	106	255	219	193	Normal	Type 4
3	2.50 ± .19	1.71 ± .13	395	615	231	217	Type 4	Type 4
4	2.33 ± .05	2.10 ± .05	45	319	196	270	Normal	Type 4
5	1.26 ± .03	0.87 ± .14	83	386	214	221	Normal	Type 4
6	0.89 ± .20	0.02 ± .025	161	228	166	155	Normal	Type 4
	$p = 0.02$[‡]		$p = 0.003$[‡]		$p = 0.6$[‡]			

* Values shown are the mean ± SD of triplicate assays. Units are micromoles of fatty acid released per milliliter of plasma per hour.
‡ Statistical significance was calculated by comparing levels on days 0 and 14 using the paired t test.
§ Phenotype was determined by lipoprotein electrophoresis.

was evaluated on six of the above patients. These patients showed a significant decrease in their total plasma lipolytic activity from a mean baseline rate of 2.1 μmol/ml/h to a day 14 rate of 1.2 μmol/ml/h ($p = 0.02$, paired t test), concomitant with a rise in plasma triglyceride levels and VLDL content (Table I). The enzymatic assay used here does not distinguish between the two lipases released after heparin injection, hepatic and lipoprotein lipase. However the preferred substrate for LPL is the VLDL class of lipoproteins, whereas hepatic lipase prefers high-density lipoproteins (33, 34). Since the triglyceride elevations seen here are due to increases in VLDL-associated triglyceride, it is reasonable to assume that the changes in lipase activity are most likely a reflection of LPL activity.

Effect of rIFN-γ on Lipase Activity In Vitro. Inhibition of LPL after rIFN-γ therapy could be due to a direct effect of rIFN-γ, or possibly to a mediator induced by rIFN-γ. To determine whether rIFN-γ directly inhibits lipase enzymatic activity, we analyzed the in vitro effect of rIFN-γ on lipase isolated from human post-heparin plasma and on cow's milk LPL. Levels of rIFN-γ ranging from 0.003 to 300 μg/ml did not decrease the enzymatic activity. We have previously reported (25) that the peak interferon levels usually detected in patients' serum, after i.m. injection of rIFN-γ at doses of 0.25–1.0 $mg/m^2/d$, are ~4–10 ng/ml.

Serum TNF Levels. An indirect mechanism of LPL suppression could involve rIFN-γ-induced production of cachectin/TNF or another monokine. At the times tested, i.e., preinjection, 4 h after the first injection, and at a single point during the second week of rIFN-γ therapy, serum TNF titers were below the limits of sensitivity of our ELISA (50 pg/ml).

Discussion

In this study, administration of rIFN-γ to cancer patients resulted in marked alterations in lipid metabolism. Hypertriglyceridemia occurred almost uniformly at doses ≥0.25 $mg/m^2/d$ (Fig. 1). Elevated triglyceride levels were associated

with increased VLDLs and decreased post-heparin lipase activity, indicating impaired triglyceride removal (Table I and Fig. 2). Since remarkably similar metabolic abnormalities have been described (3, 4) in chronic illness-induced cachectic states in animals, our observations suggest that rIFN-γ may play a role in the human body's response to malignancy. Furthermore, the serum levels of interferon achieved after injection of 0.25 $mg/m^2/d$ of rIFN-γ are in the same range (mean peak titer, 4 ng/ml or 80 U/ml [25]) as those reported (35) in pathophysiological circumstances (mean peak titer in aplastic anemia, 90 U/ml), supporting the potential relevance of these data to chronic illness in man.

This hyperlipidemia could be caused by either direct or indirect mechanisms: (*a*) suppression of lipase enzymatic activity, (*b*) reduction in lipase production, or (*c*) stimulation of macrophages to release a mediator(s) that act on lipase. In vitro preincubation of rIFN-γ at levels up to 30,000-fold greater than those usually achieved in patients' serum after i.m. injection (25) had no effect on isolated human plasma lipase activity. Therefore, interferon's actions are probably not due to direct suppression of LPL enzymatic activity. Several lines of evidence suggest the possibility of an indirect mechanism involving monokine induction. In this respect, it has been shown that activated macrophages release one or more mediators that are capable of decreasing LPL activity in vitro (16, 17), and in animals afflicted with chronic infection or cancer (12–16). IFN-γ is a powerful macrophage activator both in vitro (21) and in man (36, 37). The monokine most extensively studied in relation to this phenomenon is cachectin/TNF. Cachectin/TNF decreases LPL activity in vitro, binds to high-affinity receptors on adipocytes (16), and at the molecular level, suppresses adipocyte gene transcription (38). Since the clearance of TNF after i.v. administration in man is rapid (J. Gutterman, unpublished observations), the negative ELISAs for serum TNF in our patients do not preclude its involvement. However, in vitro data indicating that IFN-γ alone is an insufficient stimulus for cachectin/TNF release (39) argue against TNF/cachectin being the effector molecule inducing hypertriglyceridemia in our patients. Another monokine that might mediate these metabolic abnormalities is IL-1, a molecule that also inhibits LPL activity in vitro (17), and the production of which can be stimulated by IFN-γ (40). Further investigation is required to determine whether or not these monokines play an important role in rIFN-γ-induced hypertriglyceridemia. In addition, a direct effect of rIFN-γ on LPL biosynthesis cannot be ruled out as the mechanism of action.

Beutler et al. (16) have hypothesized that, in response to infection or tumor, activated macrophages may function as an "endocrine system" releasing a "hormone," i.e., cachectin/TNF and/or another monokine, that influences the behavior of adipocytes by binding to specific receptors. Therefore, secretion of immune mediators during chronic illness may serve to mobilize energy reserves from adipose cells preferentially for the immune system, and eventually result in the marked catabolic state, termed cachexia, which is a clinical hallmark of cancer. To date, the work on which these hypotheses are based has been performed in vitro and in animal models. Our observations show that rIFN-γ, a lymphokine with pleiotropic immunomodulatory properties, has a profound effect on human triglyceride regulation. Investigations of the direct effect of

interferon on lipase production, and of cachectin/TNF and other monokines on lipoproteins in cancer patients, are in progress. These studies should help delineate the mechanisms by which factors produced by the immune system modulate the control of lipid metabolism in man.

Summary

Animals suffering from malignancy or chronic infection develop characteristic metabolic abnormalities, including a well-defined hypertriglyceridemic state. These abnormalities have been attributed to release of one or more mediators from activated macrophages. We report that cancer patients receiving RIFN-γ, a potent macrophage activator, at doses of $\geq$0.25 mg/m^2/d i.m. show marked increases in triglyceride but not in cholesterol levels (pretreatment triglyceride level of 180 $\pm$ 190 mg/dl [mean $\pm$ SD] vs. a day-14 level of 370 $\pm$ 242 mg/dl, $n = 23$, $p < 0.001$ by the paired t test). This hypertriglyceridemia was characterized by an increase in very low-density lipoproteins and a decrease in plasma post-heparin lipase activity, consistent with defective triglyceride clearance (mean pretreatment lipase level of 2.1 μmol/ml/h vs. a day-14 level of 1.2 μmol/ml/h, $n = 6$, $p = 0.02$ by the paired t test). rIFN-γ did not directly inhibit lipoprotein lipase enzymatic activity in vitro. Other possible mechanisms of action, such as suppression of lipase by an rIFN-γ-induced mediator released from activated macrophages, or a direct effect of interferon on lipase biosynthesis, require further investigation. Our observations provide evidence that factors produced by the immune system can regulate lipid metabolism in man.

Note added in proof: Recent work by Patton et al. (41) showing that rIFN-γ can suppress LPL in 3T3 L1 adipocytes suggests that direct inhibition of lipase production by IFN could be the mechanism resulting in hypertriglyceridemia.

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