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Interferons and tumor necrosis factors have similar catabolic effects on 3T3 L1 cells

(lipogenesis/lipoprotein lipase/B-cell lymphotoxin/receptors)

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ABSTRACT **The effect of a variety of cytokines on lipid metabolism in 3T3 L1 mouse fibroblasts and adipocytes was studied. Uptake of [^{3}H]acetate by adipocytes and heparin-releasable lipoprotein lipase activity was inhibited after treatments of the cells with picomolar concentrations of recombinant human tumor necrosis factor α (rHuTNF-α), human tumor necrosis factor β (rHuTNF-β, also called lymphotoxin), murine interferon-γ (rMuIFN-γ), and a human hybrid interferon-α [rHuIFN-α_2/α_1 (*Bgl* II)]. Recombinant human interferon-γ (rHuIFN-γ), natural human colony-stimulating factor (HuCSF), and human interleukin 2 (HuIL-2) had no effect. Similar though less-marked suppression of [^{3}H]acetate uptake by cytokines was seen in 3T3 L1 fibroblasts. Cytokines inhibited the incorporation of [^{3}H]acetate into both membrane and storage lipids in the adipocytes. In addition to blocking lipid uptake and synthesis, rHuTNF-α and -β, and rMuIFN-γ stimulated the release of free fatty acid into the medium from adipocytes. Binding studies suggest that rHuTNF-α and rHuTNF-β compete for the same cell-surface receptor on 3T3 L1 adipocytes, while rMuIFN-γ binds to a separate receptor. The binding of rTNF-α to both adipocytes and fibroblasts can be significantly enhanced by preexposure of the cells to rMuIFN-γ. There appear to be both high- and low-affinity receptors for rHuTNF-α on adipocytes, whereas fibroblasts exhibit a single class of high-affinity receptors. These results suggest that a variety of structurally distinct cytokines possess lipid mobilization activity, which may be of critical importance to the host in defense against infection or malignancy.**

The invasion of the body by viruses, bacteria, or parasites usually elicits an integrated host response that kills and removes the infectious agents and provides immunity against future challenges. Much of the host response is modulated by a class of inducible proteins called cytokines (1–3). It is now clear that there are many distinct host cytokines that can be produced by a wide variety of cell types, including epithelial cells, fibroblasts, tumor cells, and particularly lymphocytes (lymphokines) and macrophages (monokines) (4–6). Tumor necrosis factors (TNFs), interleukins (ILs), and α-, β-, and γ-interferons (IFN-α, -β, and -γ) are representative and well-characterized cytokines. Although there is considerable structural and functional heterogeneity among these families of cytokines, they all appear to have roles in the regulation of host immunity and inflammation (7–12). When administered parenterally at high doses they can be toxic, and many of the symptoms associated with the common cold and influenza such as fever, nausea, and muscle aches can be induced by the administration of pure cytokines (13, 14). Unraveling the sequence of cytokine actions that occur during the host response to infection is very complex because (*i*) cytokines regulate the production of one another (15–17), (*ii*) an individual cell may produce many different cytokines (18, 19), and (*iii*) different cytokines may have similar bioactivities, as is the case with TNF-α, IL-1, and IFN-α, all of which appear to have direct antiproliferation activities *in vitro* (20, 21).

Two lines of research recently converged when it was discovered that a blood-borne factor (cachectin) produced in parasite-infected animals and purified from the culture supernatants of endotoxin-stimulated mouse macrophages, exhibited a high degree of sequence homology to human TNF-α (HuTNF-α) (22, 23). Cachexia, a constitutional disorder characterized by general ill health and malnutrition often accompanies a variety of diseases, including cancer and infection. Cerami and coworkers named their purified blood factor cachectin because it blocked the ability of adipocytes to synthesize and assimilate fat and thereby suggested a mechanism to explain wasting in infected animals (24, 25). They postulated that in the acute phase of infectious challenge, TNF/cachectin would induce a net flux of lipid into the circulation, where the host defense system could use it as an energy source. With chronic infectious challenge, however, wasting could persist and death would ensue (24, 25).

Because many other cytokines are synthesized and released during infection (1–3), we have studied the effects of additional cytokines on lipid metabolism. Three indices of lipid metabolism were measured: [^{3}H]acetate uptake, which provides an indication of the rate of synthesis of long-chain lipids from small molecular weight precursors; lipoprotein lipase (LPL) activity, which is an indication of the cell's capacity to take up triglyceride from the medium; and fatty acid secretion into the medium, which is an indication of cell lipid catabolism. The results of our investigations demonstrate that the ability to alter lipid metabolism is common to a variety of structurally distinct cytokines and not unique to TNF-α.

MATERIALS AND METHODS

Cytokines. Recombinant HuTNF-α (rHuTNF-α), HuTNF-β (rHuTNF-β), human interferon-gamma (rHuIFN-γ), murine interferon-γ (rMuIFN-γ), and a human hybrid interferon-α [rHuIFN-α_2/α_1 (*Bgl* II)] were produced in *Escherichia coli* and purified as described (8, 22, 26–28). Human colony-stimulating factor (HuCSF) [2200 colony-forming units (cfu)/μg] was obtained from Genzyme (Boston, MA)

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Abbreviations: IFN, interferon; TNF, tumor necrosis factor; IL, interleukin; LPL, lipoprotein lipase; CSF, colony-stimulating factor; Hu, human; Mu, murine; r, recombinant; cfu, colony-forming unit(s).

and human interleukin 2 (HuIL-2) (3400 half-maximal units/mg) was from Collaborative Research (Lexington, MA). A monoclonal rHuTNF-α antibody was prepared as described.[§]

Cell Cultures. 3T3 L1 Swiss mouse embryo fibroblasts were generously provided by Howard Green (Harvard Medical School). The cells were grown in 6- or 12-well plates at 37°C in Dulbecco–Vogt modified Eagle's medium (DVEM) containing 10% fetal calf serum as described (29). Differentiation of the 3T3 L1 fibroblasts into adipocytes was induced by treating the confluent cells for 2 days with this medium supplemented with 0.5 ml 1-methyl-3-isobutyl-xanthine/0.25 μM dexamethasone/insulin (1 μg/ml) as described (30). Cells were then refed three times per week with standard media without additives and used between the 7th to 14th day after differentiation began.

[^{3}H]Acetate and Deoxy[^{14}C]glucose Uptake. 3T3 L1 cells in 12-well plates ($\approx 5 \times 10^5$ cells per well) were washed two times with Krebs–Ringer phosphate buffer (KRP) containing fatty acid-free bovine serum albumin (1 mg/ml) and then treated with cytokine for up to 24 hr in KRP (1 ml per well) (similar results were obtained with DVEM containing 10% fetal calf serum). After cytokine treatment, 5 μl of ethanol containing 50 μCi of [^{3}H]acetate (3.4 Ci/mmol; 1 Ci = 37 GBq) (New England Nuclear) was added per well (containing 1 ml of KRP), and the cells were incubated for an additional 1 hr with periodic agitation. Tracer uptake was stopped by three 1-ml rinses of the cells with KRP. The labeled cells were solubilized in 1 ml of 0.1% $NaDodSO_4$ in 50 mM Tris·HCl, pH 7.5/50 mM NaCl/5 mM EDTA by gentle resuspension with a Pasteur pipette. Aliquots of the cell digest were taken for protein assay (50 μl), total counts (50 μl), and lipid extraction (800 μl). [^{3}H]Acetate uptake was linear for at least 60 min under the conditions used in this study (data not shown). Anti-rHuTNF-D, a rHuTNF-α neutralizing monoclonal antibody (1 μg neutralizes 10 ng of rHuTNF-α) was used at 4 times its equivalent neutralizing concentration. Uptake of 2-deoxyglucose was assayed as described (30) and was linear for at least 60 min (data not shown).

Lipids were extracted from the $NaDodSO_4$ cell homogenate according to the method of Folch *et al.* (31) in 6-ml glass test tubes with Teflon-lined caps. Lipids were isolated from the lower phase, dried under a stream of nitrogen, and then resuspended in 1 ml of chloroform/methanol (2:1; vol/vol). Aliquots (50–100 μl) of the solubilized lipids were analyzed by thin-layer chromatography (TLC) on Silica Gel 60 TLC plates (Whatman) in a solvent system of petroleum ether/ethyl ether/acetic acid (80:20:1; vol/vol). Lipid classes were visualized by exposure to iodine vapors, and spots were circled with a pencil and scraped into scintillation vials and counted in 10 ml of Econofluor (New England Nuclear).

In some experiments, adipocytes were labeled with [^{3}H]acetate (50 μCi per well) for 24 hr in KRP and then rinsed three times to remove tracer in the medium. The radioactive cells were then treated with cytokine or phosphate-buffered saline (PBS), and the release of radioactive free fatty acid into the medium [KRP/bovine serum albumin (40 mg/ml)] was followed over time. Lipids were extracted from the medium according to Folch *et al.* (31). An aliquot (50 μl) of the lipid extract was counted and then the remainder was concentrated, separated into classes by TLC, scraped, and counted as described above.

Binding of ^{125}I-Labeled TNF-α and Insulin to 3T3 L1 Cells. The specific binding of ^{125}I-labeled rHuTNF-α (2×10^5 cpm per well) to 3T3 L1 cells with or without preincubation of the cells with rMuIFN-γ (59 nM) for 24 hr was measured as described (32). Binding to cells (5×10^5 cells per well) of ^{125}I-labeled rHuTNF-α in the presence of variable concentrations of unlabeled ligand was allowed to take place for 2 hr at 37°C. Cells were then washed three times with McCoy's 5A medium and solubilized with 0.1% $NaDodSO_4$. Cell-bound radioactivity was counted in a γ counter. Insulin binding was measured as described (30). Experiments were conducted in triplicate in 12-well plates.

LPL Assay. The effect of cytokines on heparin-releasable LPL activity from 3T3 L1 adipocytes was determined after 16 hr of exposure to the cytokines. Exposed cells were washed twice in KRP and incubated for 60 min at 37°C in 40 ml of buffer containing 2 units of heparin. An aliquot of buffer (1 ml), containing released LPL activity was then incubated with 200 μl of a [^{14}C]triolein-labeled triglyceride substrate for 60 min at 37°C. The reaction was terminated and analyzed as described (33, 34).

Protein and Triglyceride Determinations. Protein was determined (35) using bovine serum albumin as a standard. Triglyceride was measured (36) using a kit manufactured by Pierce.

RESULTS

[^{3}H]Acetate and Deoxy[^{14}C]glucose Uptake by 3T3 L1 Cells. Both human and murine cytokines were used in this study of murine 3T3 L1 cells. Although TNFs react efficiently across species boundaries (21), this is not the case for IFNs with the exception of a unique hybrid human IFN-α (see below) (26). Fig. 1 shows the effect of rMuIFN-γ, rHuTNF-α, and rHuTNF-β on [^{3}H]acetate uptake in 3T3 L1 adipocytes. All three cytokines inhibited uptake in a dose-dependent manner. rHuTNF-α and -β exhibited similar dose–response curves [IC_{50} (concentration for 50% inhibition), $\approx$4 pM]. rMuIFN-γ was not quite as potent as rHuTNF-α or -β (IC_{50}, $\approx$171 pM). Time course studies (not shown) indicated that the

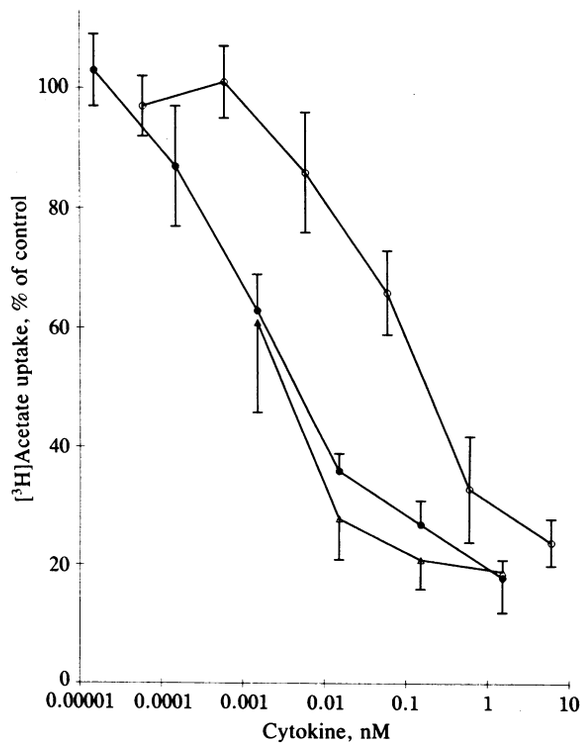

FIG. 1. Effect of cytokine dose on uptake of [^{3}H]acetate by 3T3 L1 adipocytes. Cells were treated with cytokines for 24 hr and then labeled with [^{3}H]acetate for 1 hr. Each point is the mean ± SD of three determinations. ○, rMuIFN-γ; ●, rHuTNF-α; △, rHuTNF-β.

[§]Bringman, T. S., Benton, C. V. & Aggarwal, B. B. (1985) *Proc. 13th Int. Congr. Biochem.*, August 25–30, 1985, Amsterdam.

inhibition of [^{3}H]acetate uptake developed gradually over the first 8–12 hr. When adipocytes were exposed to rHuTNF-α (1.5 nM) for only 1 hr and then rinsed three times, [^{3}H]acetate uptake was inhibited 62.2% ± 2.4% (n = 3) 24 hr later. Thus, the length of time of adipocyte exposure to cytokine that is required to elicit inhibition may be brief.

To determine whether cytokine treatments were affecting cell viability, uptake of 2-deoxyglucose in treated and untreated adipocytes was measured (Table 1). Neither rHuTNF-α nor rMuIFN-γ appeared to significantly affect 2-deoxyglucose uptake in basal and insulin-stimulated adipocytes, which indicates that the treated cells were viable and had an intact glucose transport system. Although rMuIFN-γ appeared to slightly inhibit uptake in control cells, it slightly stimulated uptake in insulin-treated cells. Chromium-51 uptake (not shown) and insulin binding by the adipocytes (Table 1) were also unaffected by 24-hr cytokine treatment.

The effect of rHuTNF-α on [^{3}H]acetate uptake by 3T3 L1 cells is compared to that of other cytokines in Table 2. rMuIFN-γ showed 90% inhibition against the murine adipocytes, in contrast to the rHuIFN-γ control, which demonstrated no effect. However, rHuIFN-α_2/α_1 (*Bgl* II), which does exhibit cross-species antiviral activity, also inhibited [^{3}H]acetate uptake. Neither HuCSF nor HuIL-2 affected uptake (Table 2). Uptake of [^{3}H]acetate by undifferentiated adipocytes (3T3 L1 fibroblasts) was also inhibited by rHuTNF-α and -β and rMuIFN-γ (35–40%), although not as markedly as in the differentiated cells. Table 2 also shows that monoclonal antibody to rHuTNF-α can block its ability to inhibit [^{3}H]acetate uptake. This result proves that the observed effects are due to the cytokine and not a bacterial contaminant.

[^{3}H]Acetate was incorporated by adipocytes primarily into the lipid fraction (78.6% ± 1.8% of total; n = 6). After rHuTNF-α and rMuIFN-γ treatment, incorporation into lipids was 60.3% ± 5.6% (n = 3) and 66.7% ± 10.5% (n = 3) of the total, respectively. Table 3 shows the relative incorporation of [^{3}H]acetate into the different classes of adipocyte lipid following 24-hr treatment with PBS, rHuTNF-α, rHuTNF-β, and MuIFN-γ. Incorporation into all classes of lipids was inhibited by the cytokines, but triglycerides showed the greatest reduction. In a separate experiment, triglyceride pool size was reduced by a 16-hr treatment with rHuTNF-α (controls, 1.00 ± 0.01 mg per well; rHuTNF-α, 0.85 ± 0.04 mg per well; n = 4). This indicates that triglycerides were still being mobilized by the adipocytes, although the pool size was not being replenished by new synthesis.

Lipoprotein Lipase Activity of 3T3 L1 Adipocytes. In addition to examining the effect of cytokines on the ability of adipocytes to synthesize lipids, their ability to take up triglyceride from the medium was assessed by measuring heparin-releasable LPL activity (≈60% of cell-associated activity). Fig. 2 shows the effect of dose of rHuTNF and rMuIFN-γ on heparin-releasable LPL activity of 3T3 L1 adipocytes. Control cells released an average of 145 ± 23 units of LPL per hr of heparin exposure per mg of protein (n = 4; ±SD) (1 unit = 1 μM oleic acid per hr). Exposure to both cytokines (16 hr) markedly decreased the level of LPL activity. rHuTNF-α was ≈1 log unit more potent an inhibitor than rMuIFN-γ [IC_{50}, ≈28 pM (rHuTNF-α); IC_{50}, ≈285 pM (rMuIFN-γ)]. The cytokines also decreased the levels of residual intracellular LPL and the LPL secreted into the medium during the cytokine incubation (data not shown).

Table 1. Effect of cytokines on 2-deoxyglucose uptake and insulin binding in 3T3 L1 adipocytes*

	Basal†	Insulin (50 ng/ml)†	Insulin bound‡
Control	8.9 ± 0.4§	30.0 ± 1.1	2.45 ± 0.06
rHuTNF-α (59 nM)	8.8 ± 0.5	29.7 ± 0.7	2.42 ± 0.07
rMuIFN-γ (59 nM)	7.1 ± 0.4	33.5 ± 1.3	2.63 ± 0.07

*Incubation with cytokines for 16 hr.
†Expressed as nmol per well per 20 min.
‡Expressed as fmol per well.
§n = 3 (±SEM).

Table 2. Effect of cytokines on [^{3}H]acetate uptake in 3T3 L1 adipocytes and fibroblasts

Cytokine	Acetate uptake, pmol per hr per mg of protein
3T3 L1 murine adipocytes	
Control	53.6 ± 9.7*
rHuTNF-α	4.6 ± 0.6†
rHuTNF-α + rHuTNF-α antibody	57.6 ± 8.9
rHuTNF-β	4.0 ± 0.4†
rMuIFN-γ	5.3 ± 0.4†
rHuIFN-γ	53.7 ± 7.7
rHuIFN-α_2/α_1 (*Bgl* II)	4.9 ± 0.4†
rHuCSF	49.5 ± 10.9
rHuIL-2	47.9 ± 5.3
3T3 L1 murine fibroblasts	
Control	8.0 ± 0.5
rHuTNF-α	5.2 ± 1.0‡
rHuTNF-β	4.5 ± 0.6§
rMuIFN-γ	5.2 ± 0.8‡

Cells were treated with cytokines (≈1.5 nM) for 24 hr then given [^{3}H]acetate for 1 hr.
*Mean ± SD (n = 3).
†$P < 0.0001$ relative to control value.
‡$P < 0.005$ relative to control value.
§$P < 0.025$ relative to control value.

Fatty Acid Release by 3T3 L1 Adipocytes. To determine the effect of cytokines on adipocyte lipolysis, adipocytes were labeled with [^{3}H]acetate for 24 hr and then treated with rHuTNF-α, rHuTNF-β, rMuIFN-γ (1.5 nM), or PBS, and the amount of radiolabeled free fatty acid released into the medium was measured at 8 and 24 hr. The results shown in Table 4 indicate that all of the cytokines tested caused ≈2-fold increase in the efflux of fatty acids into the medium compared to control cells at both 8 and 24 hr.

rHuTNF-α Binding to 3T3 L1 Cells. The specific binding of ^{125}I-labeled rHuTNF-α to differentiated and undifferentiated 3T3 L1 cells was studied in control cells and in cells that had been exposed to rMuIFN-γ (59 nM) for 24 hr (Fig. 3). Preexposure of ME-180 cells to rHuIFN-γ had been shown to induce rHuTNF-α receptors (32). 3T3 L1 adipocytes bound more than twice as much rHuTNF-α as 3T3 L1 fibroblasts (Fig. 3 *A* and *C*). The binding of rHuTNF-α to both cell types

Table 3. Incorporation of [^{3}H]acetate into different lipid classes of 3T3 L1 adipocytes after 24-hr exposure of cells to 1.5 nM cytokines

Lipid class	PBS	rHuTNF-α	rHuTNF-β	rMuIFN-γ
Phospholipid	1.1 ± 0.5	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.1
Cholesterol	4.5 ± 0.1	1.0 ± 0.2	0.8 ± 0.1	1.2 ± 0.3
Fatty acid	2.0 ± 0.2	0.8 ± 0.1	0.7 ± 0.1	1.1 ± 0.1
Triglyceride	42.9 ± 0.4	2.0 ± 0.1	2.0 ± 0.1	2.6 ± 0.1
Glycerol ethers	2.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
Cholesterol esters	0.9 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.2

Cells were allowed to take up acetate for 1 hr after cytokine treatment. Results are expressed as pmol of [^{3}H]acetate incorporated per hr per mg of protein (mean ± SD of three determinations).

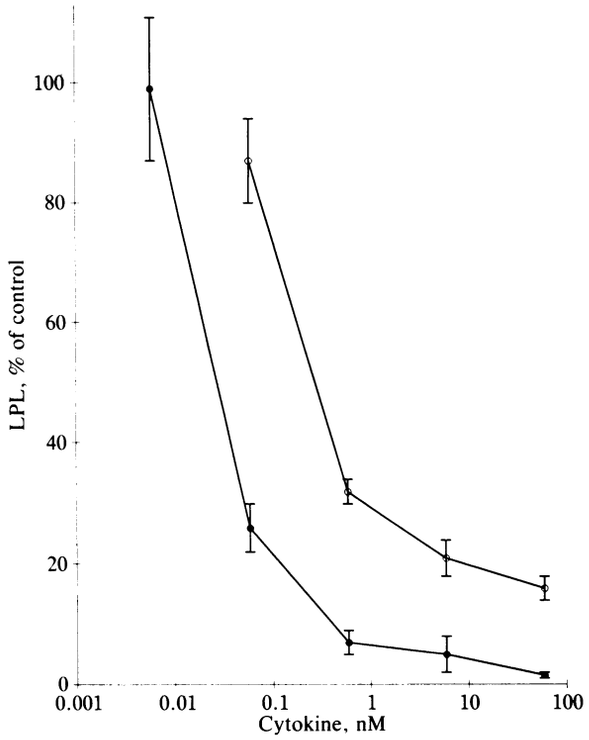

FIG. 2. Effect of cytokine dose on heparin-released LPL activity by 3T3 L1 adipocytes after 16 hr of exposure to the cytokine. Each point is the mean ± SEM of pooled data from three separate experiments. ●, rHuTNF-α; ○, rHuIFN-γ.

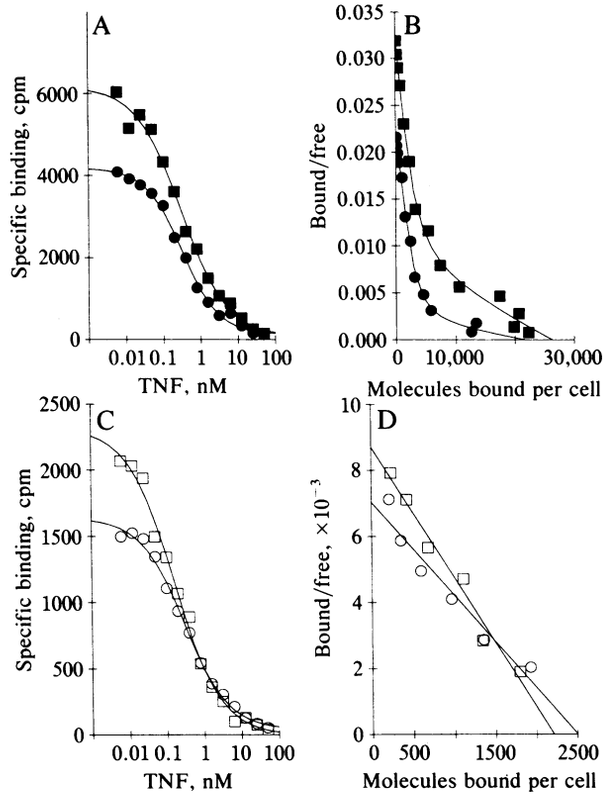

FIG. 3. Analysis of rHuTNF-α receptors on 3T3 L1 fibroblasts and adipocytes. Specific binding of ^{125}I-labeled rHuTNF-α to adipocytes (*A*) and Scatchard analysis (*B*). Specific binding of ^{125}I-labeled rHuTNF-α to fibroblasts (*C*) and Scatchard analysis (*D*). Squares, rMuIFN-γ preincubation; circles, without rMuIFN-γ preincubation. Each point is the mean of three determinations.

was enhanced by preincubation with rMuIFN-γ. However, rMuIFN-γ did not compete with the binding of ^{125}I-labeled rHuTNF-α to the cells, indicating distinct receptors for the two cytokines. In contrast, 1 μM rHuTNF-β displaced bound ^{125}I-rHuTNF-α from adipocytes by ≈70%, which suggests that rHuTNF-α and -β may have the same or similar receptors on this cell line. Scatchard analyses of rHuTNF binding to 3T3 L1 adipocytes yielded a curvilinear plot (Fig. 3*B*), indicating that there are both high- and low-affinity receptors on adipocytes. 3T3 L1 fibroblasts appear to possess only high-affinity receptors (Fig. 3*D*).

DISCUSSION

The results of this study show that the ability to inhibit anabolic processes in 3T3 L1 adipocytes and fibroblasts is a common property of several different cytokines and not a unique property of TNF-α. Although rHuTNF-α and rHuTNF-β possess 30% homology in their amino acid sequences (22), they are not homologous with rHuIFN-γ or rHuIFN-α (37). Similarly, rHuIFN-γ and rHuIFN-α are distinct molecules, which appear to interact with cells at separate cell-surface receptors (38). Fibroblast IFN (IFN-β) has also been shown to inhibit [^{3}H]acetate incorporation into 3T3 L1 cells (39). Thus, all three major types of IFN possess the ability to inhibit anabolic lipid metabolism in adipocytes. Murine IL-1 appears to partially inhibit LPL activity in murine adipocytes. However, maximal inhibition is only 50% (40). The failure of HuIL-2 and HuCSF to suppress murine adipocyte anabolism may represent simply a lack of such activity or a difference in species specificity.

Table 4. Release of free fatty acid into the medium by 3T3 L1 adipocytes incubated in the presence and absence of 1.5 nM cytokine

Treatment	Time of cytokine exposure, hr	Free fatty acid released, cpm per well	
PBS	8	11,865 ± 3,910	
rHuTNF-α	8	35,898 ± 21,809	$P < 0.025$
PBS	8	28,674 ± 12,254	
rHuTNF-β	8	60,747 ± 17,439	$P < 0.005$
PBS	8	27,046 ± 12,129	
rMuIFN-γ	8	42,505 ± 23,465	$P < 0.200$
PBS	24	66,571 ± 17,282	
rHuTNF-α	24	126,122 ± 91,964	$P < 0.200$
PBS	24	87,798 ± 28,057	
rHuTNF-β	24	307,632 ± 107,744	$P < 0.005$
PBS	24	95,951 ± 37,627	
rMuIFN-γ	24	197,832 ± 10,331	$P < 0.005$

Each treatment had its own control (PBS) in the same plate. Results are expressed as mean ± SD of five or six determinations.

Cerami and coworkers' results suggest that MuTNF has no direct effect on lipolytic enzymes, but instead acts by regulating the level of transcription of the genes encoding them (41, 42). Our results show that secretion of free fatty acids by adipocytes is stimulated by rHuTNF-α and -β and rMuIFN-γ. Thus, these cytokines appear to suppress lipid anabolism and enhance secretion of free fatty acids.

An important focus of cytokine research is to understand the mechanism of cytotoxicity of rHuTNF-α and -β and the IFNs. Those cytokines that exhibited inhibition of lipid anabolic processes in adipocytes in this study have also been shown to be cytotoxic or cytostatic to certain cells (5, 43, 44). It is uncertain whether there is a relationship between suppression of anabolic metabolism and susceptibility to cytotoxicity. Suppression of anabolic processes, such as fatty acid synthesis, may be lethal to TNF-sensitive cells that possess no fatty acid reserve for membrane biogenesis and

turnover. It is not known what distinguishes a sensitive and resistant cell type. Either can have a full complement of rHuTNF-α receptors (45). Indeed, the growth of some cell types is actually stimulated by rHuTNF-α (43).

Mobilizing host defenses against invading pathogens requires an acute source of energy to compensate for loss of appetite, mount a fever, repair inflamed tissue, and fuel other critical metabolic needs. In addition, chronic infection and malignancy also place high demands on energy supplies (25). Several of the cytokines here have been shown to be important in these situations (1–3), and their common role in lipid metabolism may benefit the host. Adipocytes occur not only in adipose tissue but scattered singly or in groups in loose connective tissue throughout the body, especially along blood vessels. We can speculate that during the multiple phases of host response to infection there is a succession of cytokines appearing and disappearing in the circulation or at the site of infection. If many of the cytokines possess lipid mobilization activity, the body will be provided with energy throughout the different phases of the infection. Alternatively, different infections (e.g., viral or microbial) or different tissues or cells in the same infection may induce a different set of cytokines (1). Thus, if energy mobilization is to occur in many types of infections or from many sites within the body, it is critical that several cytokines, with overlapping biological functions, have evolved to share this host defense activity.

Note Added in Proof. Kurzrock *et al.* have shown that rHuIFN-γ induces hypertriglyceridemia and inhibits post-heparin LPL activity in cancer patients (46).

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