Tumor Necrosis Factor, Interleukin, and Interferon Induced Changes in Lipid Metabolism as Part of Host Defense (43424)

CARL GRUNFELD[1] AND KENNETH R. FEINGOLD
Department of Medicine, University of California, San Francisco and Metabolism Section, Medical Service, Veterans Administration Medical Center, San Francisco, California 94121

The host response to infection is mediated by cytokines, hormones of the immune system that have multiple biological activities, including enhancing the recruitment, proliferation, activation, and differentiation of white blood cells (1). In addition, a wide variety of metabolic disturbances occur during infection (2); these are now also thought to be mediated by cytokines (3).

This review will focus on one such disturbance in metabolism, the hypertriglyceridemia of infection. Early work noted the simultaneous occurrence of hypertriglyceridemia and cachexia during infection leading to the hypothesis that a single factor caused both cachexia and hypertriglyceridemia by decreasing the storage of fat in adipose tissue (4). However, subsequent data indicated that cytokine-induced disturbances in lipid metabolism do not directly cause cachexia (3). In addition, research demonstrated that the liver is a primary focus for cytokine-induced disturbances in lipid metabolism *in vivo*. (3). As this field has evolved, it has become clear that there are complex interactions between the immune system and lipid metabolism. It appears that hypertriglyceridemia during infection could play a role in host defense.

Cytokines and Lipid Metabolism in Cultured Mouse Fat Cells

The observation that supernatants from endotoxin-stimulated macrophages could induce both hypertriglyceridemia and wasting in animals led to a search for the factor thought to be responsible for cachexia (cachectin) (4). These supernatants were found to decrease the storage of fat in cultured mouse 3T3-L1 fat cells by decreasing lipoprotein lipase (LPL) levels, decreasing *de novo* lipogenesis, and increasing lipolysis. Cachectin was purified based on its ability to decrease LPL and was found to be tumor necrosis factor (TNF). Because a decrease in LPL could slow the clearance of plasma triglycerides, it was hypothesized that TNF might be both the mediator of cachexia and the cause of hypertriglyceridemia. However, subsequent work has demonstrated that these properties are shared by many cytokines; TNF, interleukin (IL) 1, and all three interferons can decrease LPL activity, decrease *de novo* fatty acid synthesis, and increase lipolysis in 3T3-L1 fat cells (3, 3a).

Cytokines and Lipid Metabolism *In Vivo*

Activation of macrophages produces both TNF and IL-1. Administration of either TNF or IL-1 to rats induces a rapid and sustained increase in plasma triglycerides (3, 5). The increase in plasma triglycerides induced by TNF resulted from an increase in very low density lipoprotein (VLDL) of normal composition; even in fed rats, plasma chylomicron levels were not increased (3). Subsequently, the TNF-induced VLDL is effectively processed to triglyceride-rich low density lipoprotein (LDL). When humans were given TNF during therapeutic trials, plasma triglycerides also rose (6).

Because the initial studies with crude cachectin and later recombinant TNF in cultured 3T3-L1 fat cells (3, 4) suggested that TNF might produce the increase in plasma triglycerides by decreasing LPL activity, the effect of TNF on LPL was examined *in vivo*. Although TNF administration decreases LPL in the epididymal fat pads of mice, rats, and guinea pigs, this decrease requires several hours (similar to the time course of 3T3-L1 cells), whereas plasma triglycerides rise within 45 min after TNF administration. In addition, when the effect of TNF was examined in other adipose tissue sites or in muscle, there was little effect of TNF on LPL activity; in fact, TNF increases post-heparin lipase activity in plasma (3).

Therefore, the question arose as to whether cytokines worked by decreasing the clearance of triglyceride-

[1] To whom requests for reprints should be addressed at Metabolism Section (111F), VA Medical Center, 4150 Clement Street, San Francisco, CA 94121.

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rich lipoproteins such as VLDL and chylomicrons. Administration of TNF of IL-1 under a variety of conditions does not result in a decrease in the clearance of triglyceride-rich lipoproteins in rats (3, 5).

Further studies revealed that cytokines have profound effects on hepatic lipid metabolism. TNF and IL-1 increase hepatic *de novo* fatty acid synthesis with a time course that is consistent with their ability to raise plasma triglycerides (3, 5). As a consequence, both TNF and IL-1 increase the production of VLDL by the liver (3, 5).

There are limited data on the ability of cytokines to mobilize free fatty acids *in vivo*. TNF administration causes a rapid increase in plasma free fatty acids (7); this should be contrasted with the ability of TNF to stimulate lipolysis in cultured fat cells, which requires many hours (3, 3a). In the common states in which fatty acids are mobilized from the periphery, such as fasting, exercise, or stress, the fatty acids return to the liver, where they are oxidized; however, during infection, mobilized fatty acids may be re-esterified into triglyceride and resecreted as VLDL (8). Recent data indicate that the free fatty acids acutely mobilized by TNF *in vivo* are likewise not oxidized and but rather are re-esterified into triglycerides which appear in the plasma (7). The relative contribution to VLDL secretion of increased hepatic *de novo* fatty acid synthesis and re-esterification of peripheral fatty acids varies with the diet administered (7).

Oxidation of fatty acids is accompanied by an increase in hepatic ketone bodies. Recent evidence indicates that IL-1 can decrease hepatic ketone body formation (9). Therefore, fatty acid oxidation is also decreased by IL-1, providing more fatty acid for re-esterification.

Cytokines and Hepatic Fatty Acid Synthesis

The regulation of hepatic fatty acid synthesis by cytokines has been examined in detail in mice because the interferons are species specific and we were only able to obtain interferons that were active in mice. Additionally, the small size of mice makes it possible to study cytokines that are only available in limited quantity. IL-6 and α-interferon (IFN-α), as well as TNF, lymphotoxin, and IL-1, have been shown to stimulate hepatic fatty acid synthesis in mice (3). Increased synthesis is seen within 30 min of administration and continues for many hours for most cytokines (3). Doses of TNF and IL-1 that stimulate hepatic fatty acid synthesis are similar to those that induce fever, i.e., endogenous pyrogen activity (3). Consequently, cytokine stimulation of hepatic lipogenesis most likely occurs during any physiological condition or infection that produces TNF or IL-1.

Mechanistic studies reveal that there are two separate classes of lipogenic cytokines. In the liver, the increase in fatty acid synthesis induced by TNF, IL-1, and IL-6 can be accounted for by their ability to increase hepatic levels of citrate, the major allosteric activator of acetyl-CoA carboxylase, which is the rate-limiting enzyme for fatty acid synthesis (10). The mechanism by which IFN-α stimulates hepatic fatty acid synthesis is not yet known (10). However, these two classes appear to work by complementary mechanisms, since the combination of IFN-α with either TNF or IL-1 produces synergy in low doses and additivity in high doses in stimulating hepatic lipogenesis. In contrast, there is no synergy or additivity when TNF or IL-1, two cytokines from the same class, are given simultaneously (10).

IL-4 is a cytokine that has been shown to both inhibit the induction of TNF and IL-1 and block the action of TNF and IL-1 (reviewed in Ref. 11). By itself, IL-4 has no effect on hepatic fatty acid synthesis, but IL-4 inhibits the ability of TNF, IL-1, and IL-6 to stimulate hepatic fatty acid synthesis (11). IL-4 works by blocking the ability of these cytokines to increase hepatic citrate levels. Therefore, it is not surprising that IL-4 cannot block the ability of IFN-α to stimulate hepatic lipogenesis (11). Thus, a cytokine's ability to regulate hepatic fatty acid synthesis is closely linked to its actions in the immune response.

Do Cytokine-Induced Changes in Lipid Metabolism Cause Cachexia?

It was originally proposed that cachectin (TNF) decreased adipose tissue LPL, which resulted in both decreased triglyceride clearance and inhibition of fat storage in adiopse cells; as a consequence, the effects of TNF on triglyceride metabolism might induce fat cell depletion and cachexia (4). Recent experimental data suggest that the induction of hypertriglyceridemia and cachexia are not mechanistically linked. First, in the original mouse cultured adipose cell model, the effects of cytokines could not be overcome by the addition of insulin (3). However, in many diseases associated with cachexia, hyperalimentation with hyperinsulinemia results in the storage of abundant fat without blocking the decrease in muscle mass (reviewed in Ref. 12). Second, the catabolic effects that TNF and IL-1 induce in cultured fat cells do not occur *in vivo* under conditions in which these cytokines increase plasma triglycerides. As discussed above, rather than decreasing triglyceride clearance and storage, TNF and IL-1 work by increasing hepatic lipogenesis and VLDL production. Finally, daily or twice daily injections of purified recombinant TNF induces persistent hypertriglyceridemia, but only transient weight loss due to acute anorexia; hypertriglyceridemic animals rapidly regain weight (13). A similar state is found during infection in humans. Plasma triglyceride levels are strikingly elevated in subjects with acquired immune deficiency

syndrome (AIDS) and human immunodeficiency virus infection (14, 15). However, there is no relationship between hypertriglyceridemia and wasting in AIDS (14). Patients with AIDS and persistent hypertriglyceridemia can show prolonged periods of stable body weight and body cell mass (14). High endogenous circulating levels of IFN-α appear to be responsible for the increase in plasma triglycerides in AIDS (15). Thus, cytokine-induced changes in lipid metabolism do not cause cachexia. Discussion of potential mechanisms by which cachexia might occur during infection can be found elsewhere (3, 12).

Could the Disturbances in Lipid Metabolism that Occur during Infection be Beneficial?

The data presented earlier indicate that there is a close linkage between cytokine mediation of the immune response and changes in lipid metabolism. Multiple cytokines at low doses rapidly modulate lipid metabolism, acting through multiple receptors, at multiple sites, and by multiple mechanisms. Such disturbances in lipid metabolism are found in many types of infections and have not yet been found to cause any harm. As a consequence, we have raised the question as to whether disturbances in lipid metabolism could be part of host defense. Cytokine-induced changes in heptaic lipid metabolism could be a component of the hepatic acute phase response, which is beneficial.

Several lines of evidence indicate that plasma lipoproteins can decrease the toxicity of bacteria and viruses. Chylomicrons, VLDL, β-VLDL, LDL, and high density lipoprotein can bind lipopolysaccharide (LPS); in addition, chylomicrons, VLDL, LDL, and high density lipoprotein have been shown to prevent the ability of LPS to induce fever, hypotension, or death in mice and rats (16–20). Recent data indicate that infusion of lipoproteins *in vivo* also decreases LPS-induced death (H. Harris, C. Grunfeld, K. R. Feingold, J. P. Kane, A. L. Jones, E. B. Eichbaum, G. F. Bland, and J. H. Rapp, manuscript in preparation). When VLDL from normal subjects is extracted, previously bound and sequestered LPS can be recovered (17); this LPS was most likely scavenged from the circulation during low grade endotoxinemia that occurs periodically in the circulation of normal individuals.

Likewise, a variety of viruses, including mouse retroviruses (21), Epstein-Barr virus (22), Japanese encephalitus virus (23), rabies virus, and vesicular stomatitus virus (24), bind to lipoproteins and are neutralized.

Summary and Conclusions

As the immune response is activated during infection, multiple changes in lipid metabolism, especially increased production of VLDL, occur. Many of the cytokines that mediate the immune response are able to produce such changes in lipid metabolism *in vivo*. The induction of hypertriglyceridemia or other changes in lipid metabolism during infection do not directly cause the wasting syndrome. It appears that such changes in lipid metabolism may be beneficial to the host, as lipoproteins inactivate a variety of infectious agents. Cytokine-driven hepatic VLDL production during infection most likely represents a part of the acute phase response. The body is thus able to increase serum lipids during infection, or at least maintain triglyceride-rich lipoproteins despite the anorexia of infection. In this manner, the anti-infective, protective effects of lipoproteins are maintained.

1. Grunfeld C, Palladino MA Jr. Tumor necrosis factor: Immunologic, anti-tumor, metabolic and cardiovascular activities. Adv Int Med **35**:45–71, 1990.
2. Beisel WR. Metabolic response to infection. Annu Rev Med **26**:9–20, 1975.
3. Grunfeld C, Feingold KR. The metabolic effects of tumor necrosis factor. Biotherapy **3**:143–148, 1991.

3a. Feingold KR, Doerrler W, Dinarello CA, Fiers W, Grunfeld C. Stimulation of lipolysis in cultured fat cells by TNF, IL-1 and the interferons is blocked by inhibition of prostaglandin synthesis. Endocrinology **130**:10–16, 1992.

4. Beutler B, Cerami A. Cachectin and tumor necrosis factor as two sides of the same biological coin. Nature **320**:584–588, 1986.
5. Feingold KR, Soued M, Adi S, Staprans I, Neese R, Shigenaga J, Doerrler W, Moser A, Dinarello CA, Grunfeld C. The effect of interleukin-1 on lipid metabolism in the rat: Similarities to the differences from tumor necrosis factor. Arteriosclerosis Thrombosis **11**:495–500, 1991.
6. Starnes F Jr, Warren RS, Jeevanandam M, Gabrilove JL, Larchian W, Oettgen HF, Brenman ME. Tumor necrosis factor and the acute metabolic response to injury. J Clin Invest **82**:1321–1325, 1988.
7. Feingold KR, Adi S, Staprans I, Moser AH, Neese R, Verdier JA, Doerrler W, Grunfeld C. Diet affects the mechanisms by which TNF stimulates hepatic triglyceride production. Am J Physiol **259**:E177–E184, 1990.
8. Wolfe RR, Shaw JHF, Durkot MJ. Effect of sepsis on VLDL kinetics: Responses in basal state and during glucose infusion. Am J Physiol **248**:E732–E740, 1985.
9. Memon RA, Feingold KR, Moser AH, Doerrler W, Adi S, Dinarello CA, Grunfeld C. Differential effects of interleukin -1 and tumor necrosis factor on ketogenesis. Am J Physiol (in press).
10. Grunfeld C, Soued M, Adi S, Moser AH, Dinarello CA, Feingold KR. Evidence for two classes of cytokines that stimulate hepatic lipogenesis: Relationships among tumor necrosis factor, interleukin-1 and interferon-alpha. Endocrinology **127**:46–54, 1990.
11. Grunfeld C, Soued M, Adi S, Moser AH, Fiers W, Dinarello CA, Feingold KR. Interleukin-4 inhibits stimulation of hepatic lipogenesis by tumor necrosis factor, interleukin-1 and interleukin-6 but not by interferon-alpha. Cancer Res **51**:2803–2807, 1991.
12. Grunfeld C, Kotler DP. The wasting syndrome and nutritional support in AIDS. Semin Gastrointestinal Dis **2**:25–36.
13. Grunfeld C, Wilking H, Neese R, Gavin LA, Moser AH, Gulli R, Serio MK, Feingold KF. Persistence of the hypertriglyceridemic effect of tumor necrosis factor despite development of tachyphylaxis to its anorectic/cachectic effects in rats. Cancer Res **49**:2554–2560, 1989.
14. Grunfeld C, Kotler DP, Hamadeh R, Tierney A, Wang J, Pierson

MA Jr. Hypertriglyceridemia in the acquired immunodeficiency syndrome. Am J Med **86**:27–31, 1989.
15. Grunfeld C, Kotler DP, Shigenaga JK, Doerrler W, Tierney A, Wang J, Pierson RN, Feingold KR. Circulating interferon alpha levels and hypertriglyceridemia in the acquired immunodeficiency syndrome. Am J Med **90**:154–162, 1991.
16. Ulevitch RJ, Johnston AR, Weinstein DB. New function for high density lipoproteins. Their participation in intravascular reactions of bacterial lipopolysaccharides. J Clin Invest **64**:1516–1524, 1979.
17. Harris HW, Grunfeld C, Feingold KR, Rapp JR. Human VLDL and chylomicrons can protect againt endotoxin-induced death in mice. J Clin Invest **86**:696–792, 1990.
18. VanLenten BJ, Fogelman AM, Haberland ME, Edwards PA. The role of lipoproteins and receptor mediate endocytosis in the transport of bacterial lipopolysaccharide. Proc Natl Acad Sci USA **83**:2704–2708, 1980.
19. Navab M, Hough GP, VanLenten BS, Berliner JA, Fogelman AM. Low density lipoproteins transfer lipopolysaccharides across endothelial monolayers in a biologically active form. J Clin Invest **81**:601–605, 1988.
20. Munford RS, Hall CL, Lipton JM, Dietschy JM. Biological activity, lipoprotein binding behavior and *in vivo* disposition of extracted and native forms of salmonella typhimurium lipopolysaccharide. J Clin Invest **70**:877–888, 1982.
21. Sernatinger J, Hoffman A, Harman D, Kane JP, Levy JA. Neutralization of mouse xenotropic virus by lipoproteins involves binding to the virions. J Gen Virol **69**:2651–2661, 1988.
22. Chisari FV, Curtiss LK, Jensen FC. Physiologic concentrations of normal human plasma lipoproteins inhibit the immortalization of peripheral B lymphocytes by the Epstein-Barr virus. J Clin Invest **68**:329–336, 1981.
23. Shortridge KF, Ho WK, Oya A, Kobayashi M. Studies on the inhibitory activities of human serum lipoproteins for Japanese encephalitis virus. Southeast Asian J Trop Med Public Health **6**:461–466, 1975.
24. Seganti L, Grassi M, Mastromarino P, Pan'a A, Superti F, Orsi N. Activity of human serum lipoproteins on the infectivity of rhabdoviruses. Microbiology **6**:91–99, 1983.