

# Tumor Necrosis Factor and Regulation of Metabolism in Infection: Role of Systemic versus Tissue Levels (43426)

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**Abstract.** Tumor necrosis factor (TNF), a pleiotropic cytokine, is produced by macrophages and other cells in a variety of infectious and noninfectious diseases. Ultimately, the net biological effects of TNF may be either beneficial or injurious to the host. For instance, during overwhelming bacterial infection, the acute overproduction of TNF causes septic shock syndrome characterized by hypotension, organ failure, and death. Antibodies against TNF prevent and reverse these sequelae in animal models of septic shock, and their use in humans is currently under investigation in clinical trials. In another instance, TNF has been implicated as an injurious mediator in the state of malnutrition that complicates the course of chronic infection and cancer. Termed cachexia, this chronic syndrome inevitably causes the afflicted host to succumb from weight loss, anorexia, and catabolism of protein and lipid. Experimental studies of animals exposed to TNF for protracted periods indicate that this cytokine is capable of causing cachexia, and the biochemical basis for these catabolic changes has been identified. More recent data indicate that the detrimental metabolic effects of TNF are not dependent upon its circulating levels in the bloodstream, but rather are dependent upon its actions locally in vital organs (e.g., brain). Thus, the metabolic basis for cachexia in infection may be largely dependent upon the amount of cytokine produced in metabolically important tissues. As a result, circulating TNF levels in cachectic patients may not accurately reflect the metabolic state of the host, and do not correlate to weight loss. These and other studies have advanced our understanding of the role of TNF in the host response to infection, and it is hoped that this will foster the development of new therapies based on inhibiting its injurious effects. [P.S.E.B.M. 1992, Vol 200]

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**A**lthough the immune system normally protects the host against injury, there are many instances when an overabundant immunological response may be lethal. For example, anaphylactic shock to penicillin is acutely caused by an excessive immunological response to a normally innocuous antigen. Other more chronic examples of immune system-mediated injury are found in cases of multiple sclerosis and systemic lupus erythematosus. Although historically the injurious effects of acute and chronic infection have been attributed directly to the presence of the invading pathogens, recent evidence indicates that a group of immunological mediators, termed cytokines,

are overproduced during infection. Recent studies indicate that the toxicity of excessive cytokine production is pivotal in causing lethal derangements in metabolism and organ function. Tumor necrosis factor (TNF) (TNF- $\alpha$ , cachectin) is one cytokine that has been implicated in both the beneficial and injurious effects of the immunological response to infection (1-3).

TNF is initially synthesized as a plasma membrane-bound precursor that is proteolytically cleaved to the 17-kDa active moiety (4). Macrophages are probably the predominate cell source of TNF *in vivo*, but other cells, including T cells, B cells, NK cells, eosinophils, hepatic Kupffer cells, and brain astrocytes, also produce TNF when exposed to a variety of invasive stimuli. Bacterial endotoxins and enterotoxins, and antigens from fungi, parasites and viruses, are potent inducers of TNF production, suggesting that its biosynthesis by immunocompetent cells represents a central mechanism in the host response to a broad repertoire of

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pathogens. The biologically active form of TNF circulates as a trimer composed of three identical subunits, and binds to one of two types of high affinity membrane receptors present ubiquitously on nearly every cell in the body (5-7).

Like other cytokines, TNF possesses bioactive diversity in functioning as a signal to immune cell responsiveness in inflammation, a growth factor in wound healing, and a cellular cytotoxin against pathogens (reviewed in Refs. 1 and 8). When excessively produced, however, TNF is extremely toxic and is capable of killing the host either acutely (as in septic shock, Table I) or chronically (as in cachexia, Table II). Herein is a brief review of the biology of TNF toxicity in the acute and chronic metabolic responses to infection. The importance of the site of TNF production as a determinant to the net metabolic effect of TNF and the implications for future diagnosis and treatment of disease are also discussed.

### TNF in Regulation of Metabolic Responses to Septic Shock Syndrome

Septic shock syndrome represents a serious complication of invasive infection that accounts for the

**Table I.** Metabolic Responses to TNF Implicated in Septic Shock Syndrome<sup>a</sup>

System	Effects
Cardiovascular	Hypotension Myocardial suppression Decreased peripheral vascular resistance
Pulmonary	Capillary leakage syndrome Adult respiratory distress syndrome Capillary leakage with edema Leukocyte margination Respiratory arrest
Renal	Acute renal tubular necrosis
Gastrointestinal	Hemorrhagic necrosis Decreased motility and absorption
Hematological	Neutrophilia or neutropenia Increased procoagulant activity Diffuse intravascular coagulopathy Endothelial activation
Central nervous	Fever Increased sympathetic outflow Anorexia Altered hypothalamic-pituitary outflow
Metabolic	Lactic acidosis Catabolic stress hormone release (catecholamines, glucagon, ACTH, cortisol) Hyperglycemia followed by hypoglycemia Hyperaminoacidemia
Musculoskeletal	Myalgia Decreased resting membrane potential in skeletal muscle Increased skeletal muscle amino acid release

<sup>a</sup> Adapted from Ref. 2.

**Table II.** Metabolic Responses to TNF Implicated in Cachexia<sup>a</sup>

System	Effects
Cardiovascular Gastrointestinal	Dehydration Decreased motility and absorption Increased liver size and hepatic lipogenesis Acute phase protein biosynthesis Stimulated glucagon-mediated amino acid transport in hepatocytes
Central nervous	Anorexia Altered hypothalamic-pituitary outflow
Metabolic	Suppression of lipoprotein lipase Hypertriglyceridemia Increased whole-body lipolysis Net insulin resistance Catabolic stress hormone release Increased whole-body protein turnover Net losses of whole-body nitrogen and protein Hyperaminoacidemia Increased amino acid release from skeletal muscle Net losses of muscle glycogen Development of "euthyroid sick" syndrome

<sup>a</sup> Adapted from Ref. 2.

death of between 150,000 and 250,000 people per year in the United States. Previously healthy individuals may be stricken with septic shock as a complication of appendicitis, pneumonia, or meningitis, but patients with cancer, acquired immune deficiency syndrome (AIDS), or other underlying medical problems are at the greatest risk. The syndrome is characterized by falling blood pressure, inadequate perfusion of vital organs, respiratory and renal failure, diffuse coagulopathies, and tissue injury in nearly every vital organ. Death may occur within hours or after repeated bouts of hypotension, with respiratory and cardiac failure occurring over several weeks. Antibiotics do not reverse these complications, and for these reasons, septic shock syndrome is regarded as a catastrophic illness.

Three lines of evidence support the suggestion that TNF is a pivotal mediator of septic shock syndrome: (i) it is produced in both experimental models and patients with septic shock; (ii) administration of TNF to healthy animals or patients reproduces the entire spectrum of deranged homeostasis that characterizes

septic shock; and (iii) neutralizing TNF in animal models of septic shock prevents these homeostatic derangements.

Large quantities of TNF are detectable in the circulation of animals or humans after exposure to bacterial endotoxin (lipopolysaccharide) or live bacteria (9, 10). Peak TNF levels are reached within 90 min and then decline as it is cleared by the kidney or bound to either tissue receptors or circulating fragments of these receptors. Although TNF is released only sporadically into the circulation of patients with septic shock, in several clinical studies, higher serum TNF levels in patients with septic shock correlate to increased morbidity and mortality (11–15).

When pathological levels of TNF are experimentally reproduced by intravenous injection of recombinant human TNF, a state of shock and tissue injury ensues that is indistinguishable from septic shock syndrome (16, 17). Within minutes after infusion of shock-inducing doses of TNF, the blood pressure falls and metabolic acidosis occurs in association with the release of supraphysiological levels of the catabolic “stress hormones” epinephrine, norepinephrine, cortisol, and glucagon. Necropsy of animals succumbing to TNF-induced shock invariably reveals hemorrhagic necrosis of vital organs, including the kidney, adrenals, and bowel, and severe inflammation and edema of the lungs (16–18). The sensitivity to human TNF varies from mouse to dog to primate, with rodents being the most resistant, but the mechanisms underlying this species-dependent sensitivity to hTNF is unknown. Nonetheless, hTNF has been found to cause shock and tissue injury across the entire spectrum of mammalian species.

The mechanisms of TNF-induced shock and tissue injury are closely dependent upon the release of many other endogenous mediators including the stress hormones, platelet-activating factor, leukotrienes, prostaglandins, superoxide radicals, nitric oxide, interleukins, and acute phase proteins (19). Interestingly, some of these factors act to enhance or diminish the metabolic side effects of TNF. For instance, interleukin (IL) 1 and lipopolysaccharide both act by unknown mechanisms to markedly potentiate the ability of TNF to cause shock and death (20, 21). TNF occupies a central role in triggering these other factors in the cascade of metabolic responses to septicemia. The importance of TNF as a trigger is suggested by studies showing that when TNF is neutralized in overwhelming septicemia, there is also a suppression of the biosynthesis of IL-1 and IL-6 (22). Thus, although bacterial products are capable of triggering these other cytokines *in vitro*, during septicemia *in vivo*, TNF acts as a key signal to an overabundant cytokine cascade that normally occurs as part of the metabolic response to infection, and may be lethal.

The importance of TNF as a trigger to these injurious sequelae of acute septicemia is suggested by stud-

ies using anti-TNF antibodies to prevent septic shock syndrome in animals infused with lethal doses of lipopolysaccharide or live bacteria. In one study, baboons were passively immunized with monoclonal antibodies raised against human TNF and subsequently infused with a lethal dose of live *Escherichia coli* (10). Replicating bacteria were present in the bloodstream of all baboons for up to 8 hr, but no antibiotic was administered until 10 hr after the onset of bacteremia. The nonimmunized controls succumbed to septic shock within hours, but the animals immunized against TNF were protected against shock and death (10). In another study using a lesser but still lethal dose of live *E. coli*, the anti-TNF antibodies conferred a protective advantage, even when administered after the bacteria (23). Thus, the net metabolic effect of TNF during acute septicemia is to trigger a series of host responses that, if overexpressed, leads to shock, tissue injury, and death. These deleterious effects are not the direct result of the circulating bacteria themselves, since they were eliminated by neutralizing TNF, but are attributable to the release of excessive, toxic quantities of TNF.

### TNF in Regulation of Metabolic Responses to Chronic Cachexia

Chronic overproduction of TNF accompanying chronic infection and other illnesses has been implicated in the metabolic derangements of undernutrition and wasting (1, 24). Termed cachexia, this syndrome is characterized by extreme weight loss, anorexia, catabolism of vital protein and energy stores, and anemia (25, 26). In the cachectic state, the host's ability to retain vital body protein during protein-caloric deprivation is lost, so that the anorectic patient with inadequate food intake continues to burn excessive quantities of both lipid and lean tissue. The result is that many patients with cachexia complicating AIDS, chronic parasite infection, or cancer succumb not to their underlying illness, but to the effects of wasting and organ failure brought on by catabolism of body mass. The severity of the problem in treating this disorder is evidenced by the fact that an individual patient's catabolic losses may not be reversible, even when protein and calories are force-fed via intragastric tube feedings.

The same three lines of evidence implicating TNF in the pathogenesis of septic shock (above) are being investigated in metabolic studies of cachexia: (i) TNF is produced in some patients and experimental animals with cachexia; (ii) chronic overproduction is capable of triggering the metabolic derangements of cachexia; and (iii) neutralizing TNF in some models of cancer cachexia has been found to attenuate the syndrome. As will be discussed, the data implicating TNF in cachexia is less well defined than in the case of septic shock syndrome; therefore, it remains a topic of intense research interest.

TNF has been detected in the tissues and blood of patients and experimental animals with cachexia caused by chronic infection, cancer, and AIDS (27–30). Although tissue macrophages are thought to be the primary cell source, certain tumors have also been shown to produce TNF (31). Attempts to study the metabolic effects of chronic exposure to TNF have proceeded along two main lines: (i) administering recombinant TNF and (ii) implanting tumors that have been genetically engineered to continuously secrete TNF (32, 33). The metabolic effects of chronic exposure to TNF by either method has been found to cause a syndrome of classical cachexia, with weight loss, anorexia, loss of body protein and lipid, and anemia. It is interesting to note that repeated injections of recombinant human TNF induce a state of tolerization or desensitization, so that the injected host becomes resistant to the toxic side effects and does not lose weight (32). Although the biological mechanisms underlying the development of desensitization to TNF are unknown (32, 34), it has been suggested that experimentally inducing this state may confer protection against TNF toxicity during infection (35, 36). Surprisingly, tolerance does not develop when animals are chronically exposed to TNF via continuous infusion pumps or genetically engineered TNF-secreting tumors.

The mechanisms underlying the metabolic responses to TNF-induced cachexia are multiple, complex, and reviewed in detail elsewhere (2, 3, 24). Briefly stated, TNF acts directly in the brain to cause anorexia, altered regulation of hypothalamic-pituitary hormones, fever, and increased sympathetic outflow. In peripheral tissue, such as adipose, the metabolic effects of TNF are catabolic, since it acts to decrease expression of lipoprotein lipase and several lipogenic enzymes and to increase degradation of triglycerides to free fatty acids. Skeletal muscle also becomes catabolic and depleted of protein when exposed to TNF *in vivo*, and myocytes become depleted of glycogen, excrete lactic acid, and release amino acids. The net catabolism of skeletal muscle protein is not mediated directly by TNF, however, because incubation of isolated myocytes with TNF does not cause increased proteolysis. The losses of muscle protein after exposure to TNF *in vivo* appear to be due to both increased whole body protein breakdown and decreased expression of actin and myosin precursors (37, 38). The liver becomes relatively anabolic in response to TNF as evidenced by an increase in the biosynthesis of acute phase proteins, accelerated rates of lipogenesis, and enhanced transport of amino acids. The net metabolic result of these biochemical responses to TNF is an anorectic host that has increased energy requirements that are met by catabolizing muscle and lipid and transporting synthetic substrate to the liver.

Antibodies to TNF have also been experimentally employed to counter the development of cachexia (39–

42). One study reported that a polyclonal antiserum raised against murine TNF given to rats with tumor-associated cachexia resulted in improved food intake and lipid balances, but this method of passive immunization did not prevent the development of protein loss (39). Another study found that monoclonal anti-TNF antibodies given to mice with cachexia caused by TNF-secreting tumors attenuated the development of weight loss, but this improvement in body mass was associated with increases in tumor growth rates (41). By virtue of the chronic nature of the cachexia syndrome, any experimental study of this type requires long-term administration of antibodies, during which it is difficult to ascertain whether the TNF produced in tissues is completely neutralized. As discussed below, even small quantities of active TNF in a metabolically important regulatory organ may lead to a net alteration of whole body metabolism. Moreover, by analogy to the metabolic responses to septic shock, TNF triggers many other mediators in the development of cachexia, and defining the biological role of the individual factors in this complex cascade is exceedingly difficult.

Based on the available data, chronic overproduction of TNF is capable of causing the cachexia syndrome. Although the mechanisms that have been proposed for TNF's role offer an appealing paradigm for understanding the pathogenesis of cachexia, it is still not known whether TNF participates in the development of human cachexia, or whether therapy may be rationally based on inhibiting TNF in this chronic condition.

### Compartmentalized versus Systemic Production of TNF

Once TNF was identified as a pathogenic mediator of the metabolic response to infection, a great deal of interest arose in measuring serum TNF levels in infected and tumor-bearing patients. These studies were performed to verify the systemic release of this potentially lethal mediator, to guide the administration of inhibitors, and to investigate the possibility of using these levels in predicting prognosis (9, 11–15, 27–30). Unfortunately, several problems have arisen in the interpretation of these data: TNF is produced sporadically, so isolated serum measurements are not representative of net production over time; circulating receptor fragments may hamper available assays; the actions of TNF vary with the humoral milieu, since other mediators, such as IL-1, may synergistically enhance the effects of TNF, even at concentrations of TNF that are below the limits of detection for available assays; and TNF may be produced and act locally in vital tissues without ever reaching the bloodstream.

For these reasons, defining the biological behavior of TNF and other cytokines may be problematic, and perhaps warrants a conceptual framework that differs

somewhat from the way in which we define the metabolic responses to the classical endocrine hormones. For instance, although TNF is a candidate mediator of cachexia, no study in cachectic humans has shown a correlation of weight loss to TNF levels. Similarly, animals and patients are frequently found to succumb to septic shock syndrome even though the TNF levels in serum are undetectable. We recently considered the possibility that these discrepancies between serum levels and outcome might in part be explained by considering that serum levels are not the whole story. Rather, the paracrine actions of TNF in metabolically vital organs might influence whole-body metabolism and outcome (43).

To study the role of locally produced TNF in vital organs, we implanted a genetically engineered tumor that continuously secreted TNF into either the brain or hind-limb of nude mice (43). Although serum TNF levels were similarly elevated to pathological levels after tumor growth in either location, the net metabolic responses to TNF were dependent upon its site of production and not upon ambient serum levels. For instance, animals with large amounts of TNF produced locally in brain developed profound anorexia and succumbed within days and, after analysis of whole body composition, had depletion of lipid but retention of protein (Table III). By contrast, when TNF was released systemically from the hind limb tumors, anorexia did not develop, but weight loss and cachexia were observed over 6–8 weeks; body composition analysis revealed depletion of both lipid and protein, as occurs in classical cachexia. Since the effects of anorexia in the TNF-secreting brain tumors could be reversed by intracerebral injection of anti-TNF monoclonal antibodies, the evidence suggests that TNF in large quantities in brain acts locally to cause anorexia and starvation. An unexplained observation from these studies (which is also a dramatic example of how its site of production influences the net effects of TNF) was the finding that hair growth occurred in the nude mice with the TNF-se-

creting brain tumor, but not in the leg tumor-bearing animals (43). Thus, intracerebral TNF acts by unknown humoral or neuroendocrine mechanisms to trigger the appearance of fur, and this effect could not be attributable to the effects of TNF in the circulation. The net metabolic effects of TNF in these studies could not be predicted by serum levels, but rather by the body compartment in which it was produced (43).

Compartmentalized production of TNF in the central nervous system has also been studied in meningitis, AIDS, and multiple sclerosis, and, in general, serum levels do not correlate to the levels in cerebrospinal fluid (44, 45). The overproduction of TNF in this central body compartment has been implicated in the development of tissue necrosis in meningitis, anorexia and gliosis in AIDS, and inflammation and demyelination in multiple sclerosis (reviewed in Ref. 46). From these and other studies, it has become clear that TNF and other cytokines are capable of exerting many of their biological effects by acting directly in vital organs; these organs, in turn, amplify these signals and cause alterations of host metabolism. From this data, one would not expect isolated serum TNF levels to be predictive of net biological effect. It is to be hoped that better methods of quantifying TNF's presence in tissues, or perhaps of integrating its production systemically over time, will be forthcoming to provide a means of correlating TNF's production with its metabolic effect.

#### Perspective: Modulation of TNF-Induced Altered Metabolism

The evidence that TNF triggers derangements of metabolic homeostasis has prompted the use of anti-TNF antibodies in clinical trials of patients with septic shock syndrome, and these results are needed to evaluate the efficacy of this therapeutic approach. Besides direct inhibition of TNF with neutralizing antibodies, other experimental approaches for reducing TNF toxicity are being studied. TNF receptor fragments that

**Table III.** Net Metabolic Responses to TNF Are Determined by Site of Production in Different Body Compartments

	TNF produced in brain	TNF produced in leg
Blood TNF levels	Elevated	Elevated
Outcome	Death in 10–14 days	Alive at 6 weeks
Food intake	Profound, acute anorexia	Modest, late anorexia
Body composition	Lipid loss Protein sparing	Lipid loss Protein loss
Brain histology	Inflammation, gliosis, neovascularization	Normal
Hematocrit	Normal	Anemic
Skin	Hair growth	No hair growth

*Note.* The net metabolic effects of TNF are determined not by the ambient concentration of the cytokine in blood (which is similar for either tumor location). Adapted from Ref. 2.

bind and neutralize TNF have been produced using recombinant DNA technology and are being investigated in models of septic shock. Another approach is based on inhibiting the biosynthesis of TNF, and several agents, including pentoxifylline, glucocorticoids, cyclosporin A, and prostaglandin E<sub>2</sub>, are being studied in this role. Other inhibitors of the secondary mediators triggered by TNF include therapies directed against platelet-activating factor, eicosanoids, nitric oxide, and superoxide radicals. Although the future for modulating TNF-induced metabolic complications may lie in one or more of these neutralizing strategies, it is also conceivable that a state of tolerance or desensitization induced by administration of TNF might protect the host. It is hoped that a better understanding of the role of TNF in the pathobiology of altered host metabolism will prompt the development of these and other novel therapies which may prove to be efficacious in septic shock and cachexia.

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