Review Article

Tumour necrosis factor

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Summary

The recent discovery of tumour necrosis factor has been a major advance in the understanding of the biology of the immunological system. A review of this macrophage-secreted polypeptide hormone may be of special interest to clinicians because it appears to play a role in several important disease processes and holds considerable promise as a therapeutic tool.

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Tumour necrosis factor (TNF) and cachectin are names for a recently discovered macrophage-secreted polypeptide hormone which has excited great interest among clinicians.[1-4] TNF seems to play a role in the pathogenesis of several disease processes, including cachexia and endotoxic shock, and its anti-tumour properties suggest potential usefulness in cancer therapy.

Infectious and neoplastic processes have a large variety of effects on their victims, some of which are not specific. Examples are: the acute-phase response, septic shock, and cachexia. It has been suggested that most features of the acute-phase response may be due to the actions of interleukin-1 (IL-1), a protein secreted by macrophages in response to various noxious stimuli.[5] Harmful effects may thus be unintended consequences of a host response to an organism or tumour. TNF is also secreted by macrophages in response to neoplasia or infection and may mediate the syndromes of cachexia and endotoxic shock. It may thus be implicated in a remarkably wide range of diseases.

Discovery of tumour necrosis factor

In 1884 a New York surgeon, William B. Coley, noticed that when a patient with a sarcoma of the neck contracted a severe bout of erysipelas, the tumour shrank progressively and the patient remained well for at least 7 years, apparently cured.[6] Coley later found that repeated injections — directly into the tumour mass — of a mixture of killed streptococcal and *Serratia* products occasionally induced regression of inoperable sarcomas.[6] This mixture, and variations thereof, became known as Coley's toxins and for many years remained the only systemic therapy for cancer.[3] In the 1940s haemorrhagic necrosis of transplanted tumours in response to the intravenous injection of an extract from Gram-negative organisms was demonstrated in guinea-pigs and mice[7] and the active principle was later shown to be endotoxin.[7,8]

In the mid-1970s, however, the group of Lloyd Old and co-workers showed that endotoxin caused tumour necrosis by stimulating the production of a serum factor called tumour necrosis factor.[9] Macrophages were thought to be the cells probably responsible for secreting TNF in response to endotoxin.[1,2] TNF was specifically cytotoxic for many transformed cell lines *in vitro* while not affecting untransformed cells.[9]

TNF was purified in 1984[10] and TNF copy DNA (cDNA) and genes of humans, mice and rabbits were later cloned and expressed in bacteria and yeast.[1,2] Beutler *et al.*[11] noted that the *N*-termini of TNF and cachectin (see below) showed considerable sequence homology. Genetic analysis established that they were, in fact, identical substances.[12]

Discovery of cachectin

Cachexia is a state of severe wasting despite a relatively normal caloric intake. Raised serum triglyceride values (predominantly in the form of very-low-density lipoproteins) often found to be associated with malignant disease[13] and both chronic parasitic[14] and acute Gram-negative[15] infections are typical of this state. Rouzer and Cerami[14] demonstrated in 1980 that the hyperlipidaemia found in cachectic rabbits with chronic trypanosomal infection was due to suppression of lipoprotein lipase activity.

Hyperlipidaemia could also be induced in mice by injections of endotoxin, and Cerami's group showed that this resulted in the suppression of lipoprotein lipase activity and the appearance of a serum factor which suppressed lipoprotein lipase activity and itself caused hypertriglyceridaemia when injected into mice.[16] This factor, called cachectin, was produced *in vitro* only by macrophages derived from endotoxin-sensitive mice.[17] In 1985, cachectin was purified to homogeneity[18] and soon after this it was shown to be identical to TNF (see above).

Molecular biology

The TNF gene is located on the short arm of chromosome 6 within the major histocompatibility complex in man.[19,20] It is about 3 kilobases long and only 1,2 kilobases from the lymphotoxin gene in mice.[21] The 3′-untranslated region of the mRNA contains an AU-rich consensus sequence similar to that found in the mRNA of several other inflammatory peptides such as lymphotoxin, IL-1 and most interferons.[12] This sequence motif seems to play a role in the regulation of mRNA degradation[22] by acting as a binding site for a regulatory protein — which may, therefore, execute co-ordinated control over several functionally related proteins.[23] Tumour necrosis factor is produced as a precursor peptide, cleaved to its mature form (157 amino acids long in humans),[2] and secreted as a trimer of three identical, 17 kilodalton subunits linked together non-covalently (Table I).[24]

Physiology

The predominant source of tumour necrosis factor is probably the macrophage.[1,2] Macrophages isolated from all tissues examined as well as peripheral blood monocytes produce TNF in considerable quantities in response to a variety of stimuli.[18,25] Several other cell types, however, also produce TNF *in vitro* under certain conditions. These include T lymphocytes,[26] natural killer cells,[27] several Epstein-Barr virus-transformed B-cell lines,[28] and even a fibroblast cell line[29] after selection for TNF resistance.

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TABLE I. STRUCTURAL PROPERTIES OF THE TNF PROTEIN[2]

1. **Consists of three identical polypeptide subunits linked together non-covalently.**
2. **Each subunit is 157 amino acids long in humans with a molecular weight of 17,5 kD.**
3. **Synthesised as 233 amino acid propeptide which is proteolytically cleaved to the mature peptide before secretion.**
4. **Each subunit is a coiled, globular, and non-glycosylated peptide with a single intra-chain disulphide bond.**
5. **Shows 30% amino acid identity with lymphotoxin and shares the same receptor.**

In vivo studies of the kinetics of TNF production have shown that cachectin is produced in large quantities within minutes after stimulation with endotoxin.[30] In one rabbit study, the serum TNF level reached a maximum of 0,3 μM within 2 hours after which it decreased rapidly.[30] This corresponds to several milligrams TNF per kilogram body weight and would be enough to cause severe shock and even death if injected at equivalent doses directly into an animal.[31] Interestingly, isolated peritoneal macrophages contain detectable levels of TNF mRNA, which could explain the rapidity with which TNF is produced upon stimulation.[32] A recent experiment[25] has suggested that some macrophages may not actually secrete TNF but may retain it in the plasma membrane, enabling them to kill susceptible target cells in a controlled and localised manner. This may be the normal role of TNF and release of soluble TNF (possibly as a result of an excessively vigorous stimulus) may be abnormal, leading to pathological conditions such as septic shock.

Several factors, both endogenous and exogenous, have been shown to regulate TNF production directly or indirectly but there is no evidence that tumor cells or their products elicit the secretion of TNF by macrophages (Fig. 1).

Apart from the effects of endotoxin, infective organisms also stimulate TNF production in other ways, either *directly* (e.g. *Trypanosomiasis brucei brucei*,[14] viruses,[1] haematoprotozoa[1]) or *indirectly*, by amplifying the effect of endotoxin (e.g. BCG,[9] *Corynebacterium*,[1,9] and *Propionobacterium*[2]). This is called priming. Endotoxin stimulates transcriptional as well as translational steps in order to increase TNF production.[32] Endotoxin also stimulates the release by macrophages of numerous other immunoregulatory factors.[33]

Many endogenously produced substances, nearly all peptides, have been found to influence TNF production. **Corticosteroids** have long been known to protect humans and other mammals from the effects of endotoxin and Gram-negative infection provided that they are administered prior to the insult.[32,34-36] An explanation for this arises from experiments in which pretreatment (but not simultaneous treatment) of macrophages *in vitro* with fairly low doses of dexamethasone blocked endotoxin-stimulated TNF production by inhibiting both transcription and translation.[32] The production of several other inflammatory peptides produced by macrophages in response to endotoxin was also inhibited by pretreatment with corticosteroids.[37]

Gamma-interferon (γ-IFN) is a well-known activator of macrophages.[1,2] While it does not stimulate production of TNF itself, it amplifies the endotoxin-induced release of TNF by macrophages and peripheral blood monocytes,[38,39] probably by stimulating transcription.[23] Interleukin-2 (IL-2) has also been shown to stimulate production of TNF by human peripheral blood monocytes and this effect was augmented by pretreatment with γ-IFN.[39]

Specific receptors for TNF are present in the liver, kidney, spleen and gastro-intestinal tract.[30] TNF is rapidly endocytosed and degraded after binding.[30,40,41] Many cell types, both normal and transformed, have high-affinity, binding sites for TNF with half-maximal binding at concentrations as low as 90 pM.[1,2,24] γ-IFN increases expression of TNF receptors on cell surfaces by stimulating synthesis of new receptors.[42,43]

Related molecules — interleukin-1 and lymphotoxin

Lymphotoxin (also called TNF-beta) is closely related to TNF in many ways. The genes of both proteins lie a mere 1,2 kilobases apart and show significant homology.[1,44] It has therefore been suggested that the TNF and lymphotoxin genes originated by the duplication of a precursor gene with subsequent sequence divergence.[1] Despite differences in primary structure, the two proteins share the same receptor and both are cytolytic for tumour cells but not normal cells.[42] Whenever tested in the same system, lymphotoxin has the same biological effects as TNF.[45] Lymphotoxin is produced predominantly by

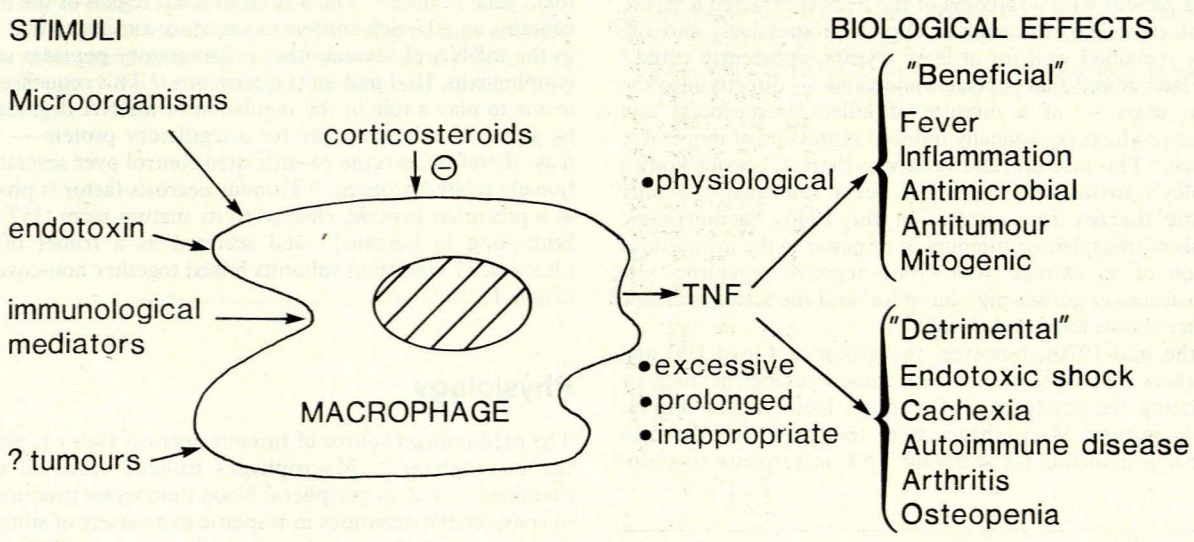

Fig. 1. Physiology of TNF. Several stimuli, both endogenous and exogenous, induce TNF secretion by macrophages (and by other cell types in lesser amounts). Pretreatment with corticosteroids inhibits this effect *in vitro*. TNF appears to have both beneficial and detrimental effects. It is suggested that the detrimental effects result from TNF production which is either excessive in amount, endures for unusually long periods, or is inappropriate either in time or place. (See text for full details and references.)

mitogen- or specific antigen-stimulated lymphocytes and its production appears to be regulated independently from TNF production at the level of gene transcription.[26]

Unlike lymphotoxin (and like TNF) IL-1 is secreted predominantly by macrophages[5] but it has no sequence similarity to TNF and does not bind to the same receptor.[4] Yet TNF and IL-1 both have remarkably similar biological activities.[4,45] Endotoxins induce and corticosteroids suppress the production of both factors.[5] TNF directly stimulates the release of IL-1 by macrophages,[46] whereas IL-1 stimulates IL-2 production which, in turn, can stimulate TNF secretion (see above).

Biological effects

The cloning and expression of the TNF gene and cDNA (see above) and the resulting widespread availability of recombinant TNF has allowed a large amount of experimental work to be done on the biological effects of TNF. The most striking conclusion to be drawn at this stage is that TNF has an enormous range of biological effects (Fig. 1).[45]

Tumour necrosis and related effects

Experimental evidence for three general mechanisms of TNF-induced tumour necrosis exists: (*i*) by the direct action of TNF either in soluble form in association with macrophages; (*ii*) by the deployment and activation of other branches of the immune system; and (*iii*) by causing ischaemia of the tumour either by inducing systemic hypotension or by promoting thrombotic occlusion of blood vessels serving the tumour (Fig. 2). It is still not known, however, which of these effects are most important in causing tumour necrosis.

Soluble TNF is selectively toxic to many transformed cells *in vitro*.[1,47] The presence of TNF receptors on target cells appears to be necessary but not sufficient for this activity, indicating that post-receptor factors are partly responsible for the variable susceptibility to TNF cytotoxicity.[43,48,49] The nature of these differences is not known but it has been noted that the presence of normal intercellular gap-junctional communication correlates with resistance to TNF cytotoxicity; manipulations which increase intercellular gap-junctional communication can confer resistance to previously susceptible cells.[50] Interferons increase the cytotoxic effect of TNF partly by increasing TNF-receptor expression in target cells but some other unknown mechanism may be more important.[43]

TNF is almost certainly the factor which enables activated macrophages to kill tumour cells selectively *in vitro*[4,51,52] even when it remains associated with the plasma membrane.[25] TNF also plays a role in the cytotoxic actions of natural killer and natural cytotoxic cells.[53,54]

Both TNF and γ-IFN cause decreased expression of the *cmyc* oncogene.[55,56] The *cmyc* protein product is known to play a role in cell proliferation and it has previously been demonstrated that suppression of this oncogene is associated with growth arrest,[56] which is precisly the effect that TNF has on several tumour cell lines.[47,55,56] Other suggested mechanisms for cytotoxic actions of TNF include induction of prostaglandins, production of free radicals and proteases and the labilisation of lysosomal membranes.[4]

Resistance to the cytolytic effects of TNF can be induced by prolonged exposure of cells to TNF and this has been correlated with loss of TNF receptors.[29] One study of various human renal cell carcinoma lines grown from a single surgical specimen showed that there was heterogeneity in the response to TNF correlating with the numbers of TNF receptors.[57] Resistance to TNF is also conferred by manipulations which improve intercellular gap-junctional communication.[50] The cytotoxic action of TNF is also modulated by heat and certain metabolic inhibitors (potentiation) and dexamethasone, phospholipase inhibitors and protease inhibitors (suppression).[4]

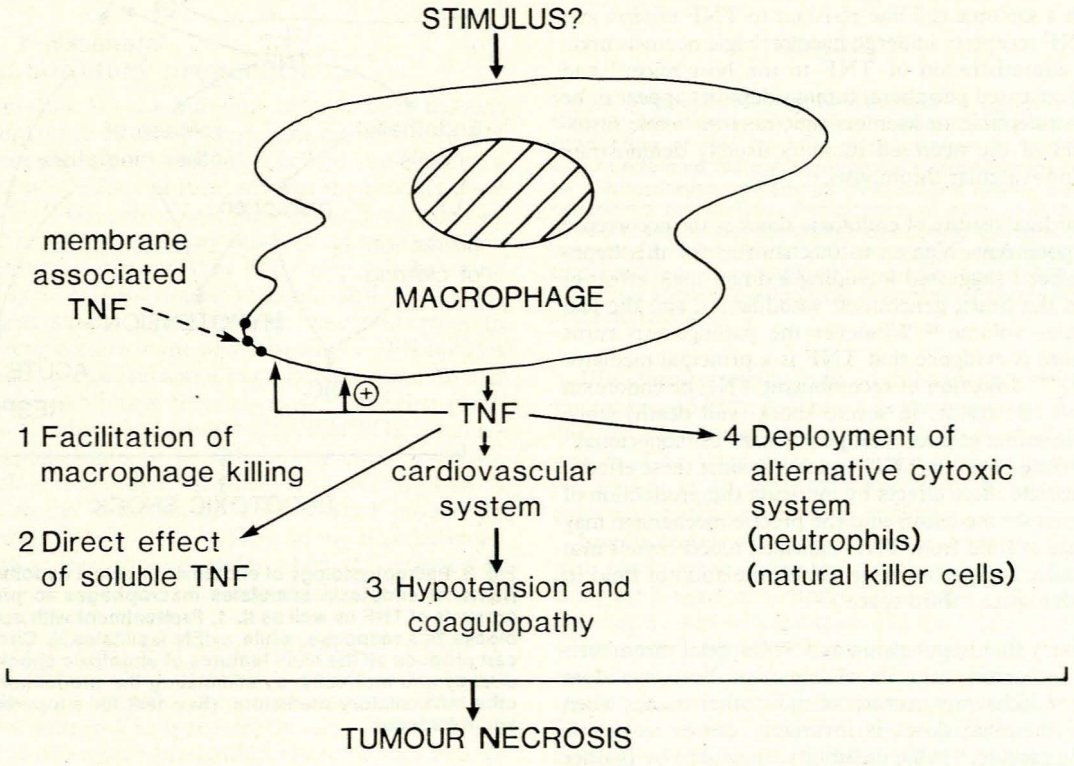

Fig. 2. Mechanisms of TNF-induced tumour necrosis. The presence of neoplastic tissue somehow stimulates TNF production by macrophages. Soluble TNF is directly toxic to tumour cells.[2] In addition, TNF facilitates macrophage killing by activating macrophages and probably also by remaining associated with the macrophage plasma membrane.[1] TNF may induce ischaemic necrosis of the tumour by inducing hypotension and a systemic coagulopathy.[3] And finally, TNF may act by deploying an alternative limb of the immune system.[4] (Evidence for all of these mechanisms is presented in the text.)

There is circumstantial evidence to suggest that part of the anti-tumour effect of TNF may be the result of interaction between TNF and cytotoxic cells. TNF activates resting T lymphocytes and macrophages.[58,59] It also induces the expression of class I and II human leucocyte antigens (HLA) on the surfaces of human tumour cells,[60] and is chemotactic for phagocytic cells.[61] In addition, TNF enhances phagocytic and cytotoxic capabilities of neutrophils,[62,63] and may also be an important regulator of various aspects of haematopoiesis.[1,45] Taken together, it is clear that TNF may, on release from macrophages or other cells, interact with various limbs of the immune system to exert its anti-tumour effects. A recent study in mice in fact demonstrated that TNF induces tumour-specific immunity against, and necrosis of, a sarcoma resistant to TNF *in vitro*.[64]

One of the best-known clinical features of endotoxic shock is the appearance of disseminated intravascular coagulation, characterised by widespread activation of the coagulation cascade leading to deposition of thrombi in small blood vessels and the consumption of coagulation factors. This effect is probably mediated by the action of endotoxin-induced TNF release followed by a direct effect of TNF on vascular endothelial cells; TNF has a wide variety of such effects, ranging from growth inhibition and toxicity to a general promotion of coagulation and inhibition of endogenous anticoagulation.[1,45,65] These effects could both increase the leakiness of blood vessels — which would contribute to hypotension — and initiate and promote clotting on endothelial surfaces. Intravenous injection of endotoxin or recombinant TNF into mice results in disseminated intravascular coagulation[31] — an effect which can be prevented by passive immunisation against TNF.[31,66] Interestingly, activated protein C (a potent endogenous anticoagulant) prevents disseminated intravascular coagulation and death when injected into endotoxin-treated primates.[67] Two lines of evidence suggest that TNF-induced disseminated intravascular coagulation may be the primary cause of *in vivo* tumour necrosis: firstly, transplanted subcutaneous tumours derived from a sarcoma cell line resistant to TNF *in vitro* and devoid of TNF receptors undergo haemorrhagic necrosis upon intravenous administration of TNF to the host mice;[67] and secondly, vascularised peripheral tumour deposits appear to be particularly susceptible to haemorrhagic necrosis while histological studies of the necrosed tumours usually demonstrate widespread intravascular thrombosis.[64]

Another cardinal feature of endotoxic shock is the occurrence of severe hypotension. Numerous mechanisms for this hypotension have been suggested including a direct toxic effect of endotoxin on the heart, generalised vasodilation, and the loss of intravascular volume.[68] Whatever the pathogenesis turns out to be, there is evidence that TNF is a principal mediator of this effect.[31,66] Injection of recombinant TNF or endotoxin into mice and rats results in severe shock (and death) while passive immunisation of mice with polyclonal[66] or monoclonal[31] antibodies directed against TNF protects against these effects. TNF may mediate these effects by inducing the production of other inflammatory mediators and the precise mechanism may involve leakage of fluid from TNF-damaged blood vessels into the extravascular compartment or an accumulation of fluid in the intracellular space ('third space').[1]

It seems likely that hypotension and widespread thrombosis could cause ischaemic necrosis of tumours. Yet, why does TNF not cause ischaemic necrosis of most other tissues when present? (In sublethal doses it invariably causes ischaemic necrosis of the caecum.[31]) One possibility, suggested by Beutler and Cerami,[1] is that tumour vasculature is peculiar and this may make tumours more susceptible to a reduction in perfusion. It is known[69] that tumours operate on a barely adequate blood supply — often outgrowing it — and have capillaries which are more fragile than normal capillaries.

Endotoxic shock

Even before the discovery of TNF it was believed that endotoxin exerted its toxic effects indirectly by inducing a response by the body involving many different parts of the immune system.[1,69–71] Recent evidence, however, implicates TNF as the central mediator of this response. Recombinant human TNF induces all the main features of endotoxaemia in rats when infused intravenously at the same dose as is produced by rats in response to equipotent doses of endotoxin.[31] In addition, passive immunisation of mice with antibodies directed against cachectin protects them from the lethal effects of infused endotoxin.[66]

Endotoxic shock involves a widespread disturbance of body function and its effects are so diverse that it is likely that TNF induces them in several ways, both directly and indirectly, by inducing the release of other inflammatory mediators such as Il-1, platelet-activating factor, and leukotrienes[1,5,46] (Fig. 3). The best understood direct effects are probably those that induce coagulopathy and hypotension. Since activated protein C infusion alone can protect against the lethal effects of endotoxin[67] and since most of the important features of endotoxic shock can be explained on the basis of a generalised decrease in tissue perfusion, these two effects (hypotension and coagulopathy) may well be the central pathophysiological events in the evolution of endotoxic shock.

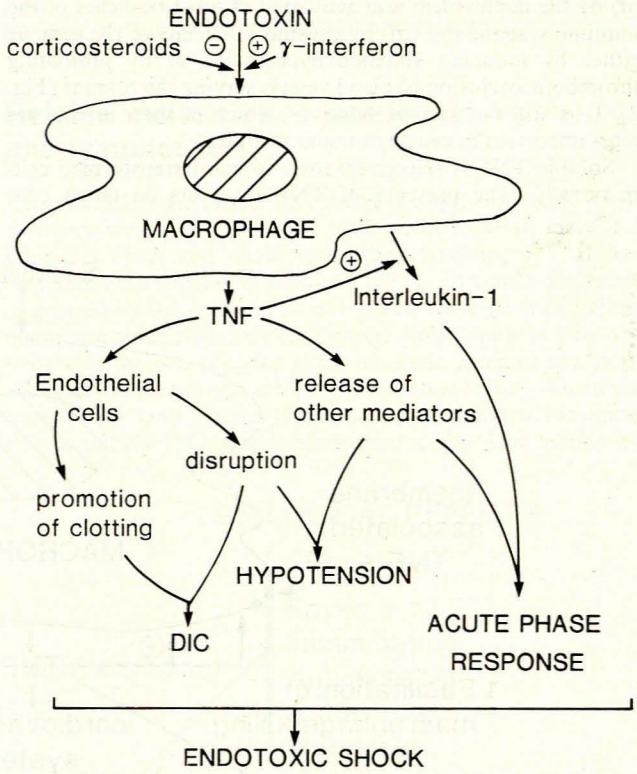

Fig. 3. Pathophysiology of endotoxic shock: a hypothetical model. Bacterial endotoxin stimulates macrophages to produce large amounts of TNF as well as IL-1. Pretreatment with corticosteroids blocks this response, while γ-IFN facilitates it. Circulating TNF can produce all the main features of endotoxic shock acting both directly and indirectly, by stimulating the production of IL-1 and othe inflammatory mediators. (See text for supporting evidence and references.)

Severe Gram-negative sepsis in humans has been associated with raised serum TNF levels[72,73] and high plasma levels of TNF in patients with serious *Neisseria meningitides* infection were associated with an adverse prognosis.[72]

Cachexia

Evidence supporting a major role for TNF in the pathogenesis of cachexia is impressive, but remains inconclusive.[4] A recent study in mice involved genetic engineering techniques used to introduce the TNF gene into a tumour cell line.[74] Introduction of TNF-producing tumour cells into mice induced a cachectic state whereas tumour cells not producing TNF had no such effect.[74] Mechanisms proposed for this effect are the following: (*a*) TNF suppresses lipoprotein lipase activity both *in vivo* and *in vitro*, and cachectic patients have reduced plasma lipoprotein lipase activity; (*b*) TNF inhibits the transcription of adipocyte-specific genes *in vitro*; and (*c*) TNF induces the mobilisation of lipid stores from adipocytes *in vitro*.[17,19,75–77] Against a primary role for TNF in cachexia are the following findings: (*a*) TNF does not seem to induce a cachectic state when injected periodically into animals and humans;[4,64] (*b*) TNF has not yet been detected in the serum of animals and humans with tumour-induced cachexia; (*c*) neither tumour cell nor their products have been shown to stimulate secretion of TNF by macrophages; and (*d*) despite the universal finding of net protein catabolism in cachectic states, TNF is unable to induce this effect even though endotoxin itself does.[4,78] One reasonable interpretation of these findings is that the development of cachexia may require the continuous presence of TNF — at levels undetectable by current techniques — in conjunction with some additional factor produced by (or in response to) tumour cells. A hypothetical model of cachexia based on these considerations is presented in Fig. 4.

Mitogenic properties

Since TNF is best known for its cytolytic and cytostatic effects on tumour cells, it came as a surprise when the substance was found to stimulate growth of several normal cell types including fibroblasts[47,79,80] and T lymphocytes.[58] TNF also stimulates synthesis and release from endothelial cells of a mitogenic protein resembling platelet-derived growth factor.[81]

Other inflammatory properties

Fever induction. Fever is currently believed to be induced by infective and other disease processes through the release of IL-1 by macrophages (and some other cells) in response to a noxious stimulus.[5,46] IL-1, in turn, induces the production of prostaglandin E_2 (PGE_2) in or near the anterior hypothalamus. PGE_2 acts on the thermoregulatory centre to cause an elevation of the thermostatic set-point. The body responds by using mechanisms such as behavioural changes, shivering, non-shivering thermogenesis and peripheral vasoconstriction to raise the core temperature to the new set-point. γ-IFN induces fever by a similar mechanism and it has now been demonstrated that TNF induces a biphasic fever response.[46] The first phase may be due to the direct induction by TNF of PGE_2 production in the hypothalamus (it is inhibited by cyclo-oxygenase inhibitors such as acetyl-salicylic acid). The second phase is probably due to the induction by TNF of IL-1 production and the subsequent direct action of IL-1 on the hypothalamus. Thus there are at least three peptides which are involved in the fever response. The possibly beneficial effects of fever have been reviewed previously.[5]

Induction of human leucocyte antigens. Cytotoxic T cells recognise foreign antigens on their target cells (which may be infected or neoplastic) only in association with HLA class I antigens. Helper T cells require the expression of HLA class II antigens on antigen-presenting cells to be activated. It is therefore interesting that TNF induces the expression of HLA class I and II antigens in human tumour cells,[60] endothelial cells, and fibroblasts.[82] TNF, together with γ-IFN, also induces HLA class II expression in pancreatic islet cells.[83] Pujol-Borrel *et al.*[83] believes that the local release of TNF and

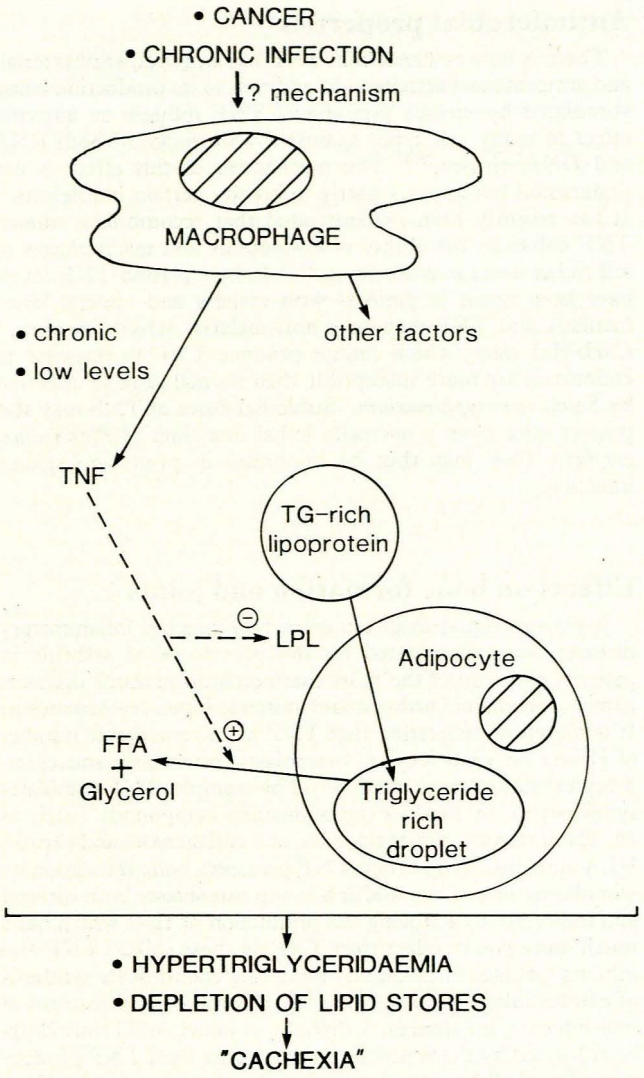

Fig. 4. Pathophysiology of cachexia: a hypothetical model. Chronic infection or cancer in the host somehow stimulates the production of TNF by host macrophages. In addition to TNF, other undefined factors produce cachexia and may be produced by macrophages or perhaps even by the tumour cells/infecting organisms themselves. Persistence of even low levels of TNF (undetected experimentally) over long periods may cause depletion of triglyceride (TG) stores in adipocytes and hypertriglyceridaemia by inhibiting lipoprotein lipase (LPL) and simultaneously stimulating lipolysis. (See text for supporting evidence and references.)

γ-IFN during a virally induced inflammatory response within the pancreatic islets may result in the inappropriate expression of HLA class II antigens on the surfaces of islet cells. This may lead to their destruction by an auto-immune process consequent to activation of autoreactive T-helper cell clones, culminating in type I diabetes mellitus.

Interactions with the immune system. TNF interacts with the immune response in numerous ways (see ref. 45 for complete list and references). Thus, both TNF production and its cytolytic actions are augmented by γ-IFN; TNF enhances many neutrophil and macrophage functions, induces HLA antigen expression, stimulates IL-1 secretion by various cell types, and activates T cells and macrophages;[59] and finally, TNF plays a role in controlling the differentiation of various leucocyte precursors. The accumulated evidence points to a role for TNF as one of the central polypeptide mediators of the immunological system.[4] Working out its exact role *in vivo*, however, is likely to be a difficult task, especially since so many of these polypeptide mediators influence each other's production and actions.

Antimicrobial properties

There is now evidence that TNF has antiviral, antibacterial, and antiprotozoal activities. In addition to its production being stimulated by viruses (see above) TNF induces an antiviral effect in many cell types against a wide range of both RNA and DNA viruses.[84,85] The mechanism of this effect is not understood but appears partly to involve certain interferons.[79] It has recently been demonstrated that recombinant human TNF enhances the ability of eosinophils and macrophages to kill *Schistosoma mansoni* larva.[59,86] Raised plasma TNF levels have been noted in patients with malaria and visceral leishmaniasis and TNF may have anti-malarial activity *in vitro*.[19] C3H/HeJ mice, which cannot produce TNF in response to endotoxin, are more susceptible than normal mice to infection by *Salmonella typhimurium*.[1] Sublethal doses of TNF may also protect mice from a normally lethal inoculum of *Plasmodium berghei*.[1] TNF may thus be important in protection against infection.

Effects on bone formation and joints

Joints are often damaged in many non-infective inflammatory diseases, as demonstrated by the prevalence of arthritis in patients with two of the most common auto-immune diseases, namely rheumatoid arthritis and systemic lupus erythematosus. It is therefore interesting that TNF has a remarkable number of effects on synoviocytes, osteoblasts, osteoclasts and chondrocytes (summarised in ref. 45). For example, TNF stimulates synoviocytes to produce inflammatory compounds (such as IL-1, interferons, prostaglandins, and collagenase) and express HLA antigens. In addition, TNF promotes bone resorption by stimulating osteoclasts and inhibiting osteoblasts both directly and indirectly by inducing the production of IL-1 which has a much more potent effect than TNF on these cells.[87] TNF also inhibits cartilage formation by inhibiting chondrocyte synthesis of extracellular matrix.[45] Many of the pathological features of non-infective inflammatory diseases of joints could thus easily be enhanced by the action of inappropriate local TNF production. The well-known genetic linkage between certain HLA alleles and auto-immune arthritis (such as rheumatoid arthritis with HLA-DR4 and the seronegative spondylo-arthropathies with HLA-B27) may be explained in part by the presence of the TNF gene within the major histocompatibility complex.

Therapeutic implications

A direct consequence of the multiple biological effects of TNF on various disease processes is the existence of numerous possible strategies to exploit these effects for clinical purposes. Some examples follow:

1. Intravenous injection of TNF alone or in combination with γ-IFN may be beneficial in the treatment of various tumours. It is theoretically likely, however, that there would be many adverse side-effects. This has in fact been demonstrated in a recent animal study in which one third of the animals died soon after injection of TNF.[88] Animals with tumours were especially susceptible — almost half of them died. The response of the tumours was disappointing. The results of studies in humans have not yet been published but are said to be disappointing as well.[4] Better results might be produced if analogues of TNF could be produced which have predominantly anti-tumour effects.

2. Low doses of TNF, or synthetic analogues thereof, may be beneficial as antimicrobial agents.

3. Antibodies to TNF or the TNF receptor may protect against both the lethal effects of endotoxic shock and the consequences of many inflammatory processes such as joint destruction, bone loss and islet cell destruction.

More possibilities will certainly emerge as more is learnt about the biology of TNF. Excessive optimism should be avoided, however, since notable therapeutic successes with peptides outside the field of endocrinology have been rare and clinical results with the interferons and interleukins, despite much initial excitement, have been disappointing as a whole.

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