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Effect of Tumor Necrosis Factor on Body Systems

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Summary

Tumor necrosis factor (TNF) is the prototypic member of a large cytokine family having two main types, tumor necrosis factor-alpha (TNF-α) and tumor necrosis factor-beta (TNF-β**).** TNF-α is the most well known multifunctional proinflammatory cytokine member of this class and is secreted mainly by macrophages. It has a number of actions on various organ systems, like hypothalamus, liver, macrophages, etc and is involved in the regulation of a wide spectrum of biological processes including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation and has been implicated in a variety of diseases, including autoimmune diseases, insulin resistance, septic shock, cancer, AIDS, multiple sclerosis, rheumatoid arthritis, trauma, malaria, meningitis, ischemia-reperfusion injury, adult respiratory distress syndrome and cancer. TNF-β is secreted by fibroblasts, astrocytes, myeloma cells, endothelial cells and epithelial cells and is a cytolytic/cytostatic and mitogen for many cells. It also inhibits the growth of osteoclasts and keratinocytes, promotes the proliferation of fibroblasts, induces metabolic acidosis and synthesis of stress hormones and alters glucose metabolism.
TNF signals through two TNF receptors, TNFR1 and TNFR2. The inhibition of TNF can mostly be achieved with monoclonal antibodies such as infliximab, adalimumab, certolizumab, pegol and golimumab, or with a circulating receptor fusion protein such as etanercept. TNF in general finds therapeutic applications in various conditions, such as psoriasis, rheumatoid arthritis, autosomal dominant polycystic kidney disease, coronary heart disease, hyperandrogenism, diabetes and many other conditions.

Key words: Tumor necrosis factor, TNF-α, TNF-β, Macrophages, Inflammation, Body functions.

Introduction

The physician William B. Coley recognized the theory of an anti-tumoral response of the immune system in vivo 100 years ago. In 1968, Dr. Gale A Granger from the University of California, Irvine, reported a cytotoxic factor produced by lymphocytes and named it lymphotoxin (LT). (1) The human TNF gene (TNFA) was cloned in 1985. (2) The sequential and functional homology of tumor necrosis factor (TNF) and LT led to the renaming of TNF as TNF-α and LT as TNF-ß. In 1985, Bruce A. Beutler and Anthony Cerami discovered that a hormone that induces cachexia and previously named cachectin was actually TNF. (3) These investigators then identified TNF as the key mediator of septic shock in response to infection. (4) Subsequently, it was recognized that TNF is the prototypic member of a large cytokine family, the TNF family.

There are two main types of TNF:

- Tumor necrosis factor-alpha (TNF-α) - the most well known member of this class, sometimes referred as tumor necrosis factor.
- Tumor necrosis factor-beta (TNF-β) - a cytokine also known as lymphotoxin.

TUMOR NECROSIS FACTOR-ALPHA

Tumor necrosis factor-alpha (TNF-α) is a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. Its primary role is in the regulation of immune cells and is able to induce apoptotic cell death, inflammation, inhibit tumorigenesis and viral replication. Dysregulation of TNF production has been implicated in a variety of human diseases, as well as cancer. (5) Recombinant TNF is used as an immunostimulant under the INN (International Nonproprietary Name) tasonermin.

Alternative Names

Cachectin
CF (cytotoxic factor)
CTX (cytotoxin)
DIF (differentiation inducing factor)
EP (endogenous pyrogens)
Hemorrhagic factor
Macrophage-derived cytotoxic factor
J774-derived cytotoxic factor
MCF (macrophage cytotoxic factor)
MCT (macrophage cytotoxin)
MD-FGF (monocyte-derived fibroblast growth factor)
PCF (peritoneal cytotoxic factor)
RCF (Released cytotoxic factor)

The new nomenclature is TNFSF2 [TNF ligand superfamily member 2], based on homology with other members of the TNF ligand superfamily of proteins.

Sources

TNF-α is a multifunctional proinflammatory cytokine secreted predominantly by monocytes/macrophages/neutrophils/T-cells/NK-cells that has effects on lipid metabolism, coagulation, insulin resistance and endothelial function. It was originally identified in mouse serum after injection with Mycobacterium bovis strain Bacillus Calmette-Guerin (BCG), endotoxin stimulated peripheral neutrophilic granulocytes, astrocytes, microglial cells, smooth muscle cells and fibroblasts. Human milk also contains this factor.

The synthesis of TNF-α is induced by different stimuli including interferons, IL2, GM-CSF, substance P, bradykinin, immune complexes, inhibitors of cyclooxygenase and platelet activating factor (PAF). Its production is inhibited by IL6, TGF-beta, vitamin D_3, prostaglandin E2, dexamethasone, cyclosporin A (CsA), and antagonists of PAF. (6)

Protein Characteristics and Structure

Human TNF- α is a non-glycosylated protein of 17 kDa having a length of 157 amino acids and forms dimers and trimers. Its homology with TNF- β is approximately 30 %.

The 17-kDa form of the factor is produced by processing of a precursor protein of 233 amino acids. A TNF-α converting enzyme has been shown to mediate this conversion. A transmembrane form of 26 kDa has been described also. TNF- α contains a single disulfide bond that can be destroyed without altering the biological activity of the factor.

TNF-α is primarily produced as a 212-amino acid-long type II transmembrane protein arranged in stable homotrimers. (7) From this membrane-integrated form the soluble homotrimeric cytokine (sTNF) is released via proteolytic cleavage by the metalloprotease TNF alpha converting enzyme TACE (also called ADAM17). (8) The soluble 51 kDa trimeric sTNF tends to dissociate at concentrations below the nanomolar range, thereby losing its bioactivity. The 17-kDa TNF protomers (185-amino acid-long) are composed of two anti-parallel β-pleated sheets with antiparallel β-strands, forming a 'jelly roll' β-structure, typical for the TNF family, but also found in viral capsid proteins.

Gene Ontology of TNF- α

Molecular function	• cytokine activity • tumor necrosis factor receptor binding • protein binding
Cellular component	• extracellular space • soluble fraction • plasma membrane • integral to membrane
Biological process	• protein import into nucleus, translocation • negative regulation of transcription from RNA polymerase II promoter • regulation of protein amino acid phosphorylation • glucose metabolic process • regulation of transcription, DNA-dependent • apoptosis • anti-apoptosis • humoral immune response • leukocyte adhesion • signal transduction • multicellular organismal development • induction of apoptosis via death domain receptors • response to virus • organ morphogenesis • regulation of cell proliferation • defense response to bacterium • positive regulation of I-kappaB kinase/NF-kappaB cascade • cellular extravasation • regulation of osteoclast differentiation • positive regulation of transcription • positive regulation of transcription from RNA polymerase II promoter • positive regulation of translational initiation by iron • negative regulation of glucose import • positive regulation of JNK cascade • regulation of immunoglobulin secretion • activation of NF-kappaB transcription factor

Receptors

A tumor necrosis factor receptor (TNFR), or death receptor, is a cytokine receptor that binds tumor necrosis factors. Because TNF is often used to describe TNF-α, TNFR is often used to describe the receptors that bind to TNF-α namely, CD120. However, several other members of this family bind to the other TNFs. (5) Two receptors for TNF have been described:

1) *TNFR1*: The 55-60 kDa has been given the designation CD120a in the nomenclature of CD antigens and is referred to as TNFRSF1A [TNF receptor superfamily member 1A]. It is expressed in most tissues, and can be fully activated by both the membrane-bound and soluble trimeric forms of TNF. The binding of TNF-α activates it in most human tissues.

2) *TNFR2*: The 75-80 kDa receptor has been given the designation CD120b in the nomenclature of CD antigens and is referred to as TNF receptor superfamily member 1B (TNFRSF1B). It is primarily expressed in immune cells and is activated by both TNF-α and TNF-β. (9) It responds to the membrane-bound form of the TNF homotrimer.

Approximately 500-10000 high-affinity receptors for TNF-α are expressed on all somatic cell types with the exception of erythrocytes. Deletion analysis in the C-terminal intracellular region of the 55-kDa receptor, TNFR1 has revealed the existence of a so-called death domain, which is involved in signaling processes leading to programmed cell death. The death domain of TNFR1 interacts with a variety of other signaling adaptor molecules, including TNFR-Associated Death Domain (TRADD) and Receptor-Interacting Protein (RIP).

The two known receptors bind both TNF-α and TNF-β. p55 is expressed particularly on cells susceptible to the cytotoxic action of TNF. p75 is also present on many cell types, especially those of myeloid. It is expressed strongly on stimulated T-cells and B-lymphocytes. The differential activities of TNF on various cell types, i.e., growth-promoting and growth-inhibiting activities, are probably mediated by the differential expression and/or regulation of multiple receptors in combination with other distinct receptor-associated proteins. p55 appears to play a critical role in host defenses against micro-organisms and their pathogenic.

A third receptor subtype is expressed in normal human liver. It binds TNF-α but not TNF-β. Some viruses contain genes encoding secreted proteins with TNF binding properties that are closely homologous to the p55 and p75 TNF receptors.

Apart from the membrane-bound receptors, several soluble proteins that bind TNF have been described. These proteins of approximately 30 kDa, called TBP-1 and TBP-2 (tumor necrosis factor binding proteins), are derived from the TNF-binding domain of the membrane receptor. They can be isolated from urine and serum and probably function as physiological regulators of TNF activities by inhibiting binding of TNF to its receptor.

Mechanism of Action and Cell Signaling

TNF-α acts via TNF Receptor (TNF-R) and is part of the extrinsic pathway for triggering apoptosis. It elicits its pro-inflammatory signals by initially binding to receptors, TNFR1 (p55) and TNFR2 (p75), on the cell surface. TNF receptors form trimers and their tips fit into the grooves formed between TNF monomers. This binding causes a

conformational change to occur in the receptor, leading to the dissociation of the inhibitory protein SODD (Silencer of Death Domain) from the intracellular death domain. This dissociation enables the adaptor protein TRADD to bind to the death domain, serving as a platform for subsequent protein binding. Following TRADD binding, three distinct signaling pathways leading to the activation of Caspases and the activation of AP-1 (Activator Protein-1) and NFκB (Nuclear Factor- kappa B) transcription factors (10) can be initiated. (11)

Activation of NF-kB: TRADD recruits TRAF2 (TNF Receptor-Associated Factor-2) and RIP. TRAF2 in turn recruits the multicomponent protein kinase IKK (IκB Kinase), enabling the serine-threonine kinase RIP to activate it. An inhibitory protein, IκBα, that normally binds to NF-κB and inhibits its translocation, is phosphorylated by IKK and subsequently degraded, releasing NF-κB. NF-κB is a heterodimeric transcription factor that translocates to the nucleus and mediates the transcription of a vast array of proteins involved in cell survival and proliferation, inflammatory response, and anti-apoptotic factors.

Activation of the MAPK (Mitogen-Activated Protein Kinase) pathways: Of the three major MAPK cascades, TNF induces a strong activation of the stress-related JNK group, evokes moderate response of the p38-MAPK, and is responsible for minimal activation of the classical ERKs (Extracellular Signal-Regulated Proyein Kinases). TRAF2 activates the JNK (Jun N-terminal Kinase)-inducing upstream kinases of MEKK1 (Mitogen-activated protein kinase kinase kinase-1) and ASK1 (Apoptosis Signal-regulating Kinase 1)(either directly or through GCKs and Trx, respectively), and these two kinases phosphorylate MKK7 (Mitogen-activated protein kinase kinase kinase 7), which then activates JNK. JNK translocates to the nucleus and activates transcription factors such as c-Jun and ATF2 (Activating Transcription Factor 2). The JNK pathway is involved in cell differentiation, proliferation, and is generally pro-apoptotic.

Induction of death signaling: Like all death-domain-containing members of the TNFR superfamily, TNF-R1 is involved in death signaling. (12) However, TNF-induced cell death plays only a minor role compared to its overwhelming functions in the inflammatory process. Its death-inducing capability is weak compared to other family members (such as Fas), and often masked by the anti-apoptotic effects of NF-κB. Nevertheless, TRADD binds FADD (Fas-Associated Death Domain) which then recruits the cysteine protease caspase-8. A high concentration of caspase-8 induces its autoproteolytic activation and subsequent cleaving of effector caspases, leading to cell apoptosis.
Cleavage of BID (BH3 Interacting Death Domain) by Caspase-8 generates tBID (Truncated BID) resulting in the disruption of the mitochondrial membrane and the release of Cytochrome-C. Binding of Cytochrome-C to APAF1 (Apoptotic Protease Activating Factor-1), allows recruitment of Caspase-9 which cleaves Caspase-3 creating its active form. The activation of Caspases at this stage of the signaling pathway can be inhibited by XIAP (X-linked inhibitor of apoptosis). (13)

Physiology

TNF is produced mainly by macrophages. It is produced also by a broad variety of other cell types including lymphoid cells, mast cells, endothelial cells, cardiac myocytes, adipose tissue, fibroblasts and neuronal tissue. Large amounts of TNF is released in response to lipopolysaccharide, other bacterial products and Interleukin-1 (IL-1).
It has a number of actions on various organ systems, generally together with IL-1 and Interleukin-6 (IL-6):

On the hypothalamus:

- stimulates the hypothalamic-pituitary-adrenal axis by stimulating the release of corticotropin releasing hormone (CRH).
- suppresses appetite.
- fever.

On the liver:

- stimulates the acute phase response, leading to an increase in C-reactive protein and a number of other mediators.
- induces insulin resistance by promoting serine-phosphorylation of insulin receptor substrate-1 (IRS-1), which impairs insulin signaling.
- potent chemoattractant for neutrophils, and helps them to stick to the endothelial cells for migration

On macrophages:

stimulates phagocytosis, and production of IL-1 oxidants and the inflammatory lipid prostaglandin E2 PGE_2

On other tissues:

increases insulin resistance.

A local increase in concentration of TNF cause the cardinal signs of inflammation (heat, swelling, redness, and pain) to occur, whereas high concentrations of TNF induce shock-like symptoms. The prolonged exposure to low concentrations of TNF results in cachexia, a wasting syndrome. This can be found, for example, in cancer patients. (6)

Pharmacology

Tumor necrosis factor promotes the inflammatory response, which in turn, causes many of the clinical problems associated with autoimmune disorders such as:

- Rheumatoid arthritis
- Ankylosing spondylitis
- Inflammatory Bowel Disease
- Psoriasis and
- Refractory asthma.

These disorders are sometimes treated by using a TNF inhibitor. Human TNF-α is active on murine cells with a slightly reduced specific activity. In general, TNF-α and TNF-β display similar spectra of biological activities in vitro systems, although TNF-β is often less potent or displays apparent partial agonist activity. (6)

Biological Activities

TNF-α show a wide spectrum of biological activities as:

- It causes cytolysis and cytostasis of many tumor cell lines. Sensitive cells die within hours after exposure to picomolar concentrations of the factor.
- It induces hemorrhagic necrosis of transplanted tumors. Within hours after injection, it leads to the destruction of small blood vessels within malignant tumors.
- It enhances phagocytosis and cytotoxicity in neutrophilic granulocytes and also modulates the expression of many other proteins, including fos, myc, IL1 and IL6.
- The 26-kDa form of TNF is found predominantly on monocytes and T-cells after cell activation. It is also biologically active and mediates cell destruction
- TNF- α in combination with IL1 is responsible for many alterations of the endothelium.
- It inhibits anticoagulatory mechanisms and promotes thrombotic processes and therefore plays an important role in pathological processes such as venous thromboses, arteriosclerosis, vasculitis and disseminated intravasal coagulation .
- It is a potent chemoattractant for neutrophils and increases their adherence to the endothelium.
- Although TNF inhibits the growth of endothelial cells in vitro, it is a potent promoter of angiogenesis in vivo.
- It is a growth factor for normal human diploid fibroblasts. It promotes the synthesis of collagenase and prostaglandin E2 in fibroblasts.
- In resting macrophages TNF induces the synthesis of IL1 and prostaglandin E2.
- It stimulates phagocytosis and the synthesis of superoxide dismutase in macrophages.
- TNF activates osteoclasts and thus induces bone resorption.
- It inhibits the synthesis of lipoprotein lipase and thus suppresses lipogenetic metabolism in adipocytes.
- It stimulates the expression of class 1 and II HLA and differentiation antigens.
- It stimulates the production of IL1, colony stimulating factors, IFN-gamma and arachidonic acid metabolism.
- It also stimulates the biosynthesis of collagenases in endothelial cells and synovial cells.
- It promotes the proliferation of astroglial cells and microglial cells and therefore may be involved in pathological processes such as astrogliosis and demyelinisation.
- It enhances the proliferation of T-cells induced by various stimuli in the absence of IL2.
- The functional capacities of skin Langerhans cells are also influenced by TNF-α.
- It is required also for normal immune responses and is the major mediator of cachexia observed in tumor patients.
- TNF is also responsible for some of the severe effects during Gram-negative sepsis. (17)

Clinical Significance and Applications of TNF- α

In contrast to chemotherapeutic drugs, TNF-α specifically attacks malignant cells. Extensive preclinical studies have documented a direct cytostatic and cytotoxic effect of

TNF-α against subcutaneous human xenografts and lymph node metastase, as well as a variety of immunomodulatory effects on various immune effector cells, including neutrophils, macrophages and T-cells. The combined use of TNF and cytotoxic or immune modulatory agents, particularly IFN-gamma and possibly IL2, is advantageous in the treatment of some tumors. In some cases, intratumoral application of TNF has been found to be of advantage in tumor control. It is used to increase the aggressiveness of lymphokine-activated killer cells. Since TNF-α is found in the synovial fluid of patients suffering from arthritis, these inhibitors may be helpful in ameliorating the disease. They may ameliorate also the severe consequences of Systemic inflammatory response syndrome. It appears to be an important autocrine modulator promoting the survival of hairy cell leukemia cells. It may be important, therefore, in the pathogenesis of this disease. It also induces significant enhancement of the number of metastases in the lung. Low doses of endogenous TNF or administration of TNF during cytokine therapy enhances the metastatic potential of circulating tumor cells. It protects hematopoietic progenitors against irradiation and cytotoxic agents, suggesting that its potential therapeutic application in aplasia induced by chemotherapy or bone marrow transplantation. TNF-α also seems to serve as a mediator in various pathologies, e.g., Septic shock, Cancer, AIDS, Transplantation rejection, Multiple Sclerosis, Diabetes, Rheumatoid arthritis, Trauma, Malaria, Meningitis, Ischemia-Reperfusion Injury and Adult Respiratory Distress Syndrome. (14)

Systemic Effects of TNF-α in Acute Exposure Vs. Chronic Exposure

ACUTE, HIGH DOSE	CHRONIC, LOW DOSE
Shock and tissue injury	Weight loss
Catabolic hormone release	Anorexia
Vascular leakage syndrome	Protein catabolism
Adult respiratory distress disorder	Lipid depletion
Gastrointestinal necrosis	Hepatosplenomegaly
Acute renal tube necrosis	Subendocardial inflammation
Adrenal hemorrhage	Insulin reisistance
Decreased muscle membrane potentials	Enhanced rate of tumor metastic
Disseminated intravascular coagulation	Acute phase protein release
Fever	Endothelial activation

Adapted from Tracey K, 1994. (15)

TUMOR NECROSIS FACTOR-BETA

Tumor necrosis factor-beta (TNF-β) is a lymphokine cytokine. It is a protein that is produced by "killer" CD8+ T cells that kill the virally infected cells by producing holes in the cell membrane. (16)

Alternative Names

Coley's toxin
CTX (cytotoxin)
DIF (differentiation inducing factor)
F-1 (factor-1)
Hemorrhagic factor
LT (lymphotoxin = LT-alpha)
Necrosin
NKCF (natural killer cytotoxic factor)
NK-CIA (Natural killer colony-inhibiting activity)

The new nomenclature is TNFSF1 [TNF ligand superfamily member 1], based on homology with other members of the TNF ligand superfamily of proteins.

Sources

TNF-β is produced predominantly by mitogen-stimulated T-lymphocytes and leukocytes and also by fibroblasts, astrocytes, myeloma cells, endothelial cells, epithelial cells and a number of transformed cell lines. Its synthesis is stimulated by interferons and IL2. Some pre-B-cell lines and Abelson murine leukemia virus-transformed pre-B-cell lines constitutively produce TNF- β. (16)

Protein Characteristics and Structure

TNF-β is a protein of 171 amino acids. It is N-glycosylated at position 62. Some cell lines secrete different glycosylated forms of the factor that may differ also in their biological activities. The protein does not contain disulfide bonds and forms heteromers with LT-β that anchors the complexes in the membrane. TNF-β and TNF-α show approximately 30 % sequence homology. Murine and human TNF-β is highly homologous (74 %). Recombinant human proteins with deletions of 27 amino acids from the N-terminus appear to be biologically active in several bioassays.
The gene has a length of approximately 3 kb and contains four exons. It encodes a primary transcript of 2038 nucleotides yielding an mRNA of 1.4 kb. The gene maps to human chromosome 6p23-6q12 approximately 1.2 kb apart from the TNF-α gene. However, both genes are regulated independently. The 5' region of the TNF-β promoter contains a poly (dA-dT)-rich sequence that binds the non-histone protein HMG-1 which is involved in the regulation of the constitutive expression of the gene. (16)

Receptors

TNF- β binds to the same receptors as TNF-α (TNFR1 and TNFR2). (16)

Biological Activities

TNF-β acts on a plethora of different cells. This activity is not species-specific. Human TNF-β acts on murine cells but shows a slightly reduced specific activity. In general,

TNF-β and TNF-α display similar spectra of biological activities in vitro systems, although TNF-β is often less potent or displays apparent partial agonist activity.

- TNF-β induces the synthesis of GM-CSF, G-CSF, IL1, collagenase and prostaglandin E2 in fibroblasts.
- It is cytolytic or cytostatic for many tumor cells.
- In monocytes it induces the terminal differentiation and the synthesis of G-CSF.
- It is a mitogen for B-lymphocytes.
- In neutrophils TNF-β induces the production of reactive oxygen species. It is also a chemoattractant for these cells, increases phagocytosis and increases adhesion to the endothelium.
- It inhibits the growth of osteoclasts and keratinocytes. Although TNF-β binds to the same receptor as TNF-α, it is not involved in the establishment of an endotoxin shock.
- TNF-β promotes the proliferation of fibroblasts and is involved probably in processes of wound healing.
- Hemorrhagic necrosis of tumors induced by TNF-β in vivo is probably the result of an inhibition of the growth of endothelial cells and the activity of TNF-β as an anti-angiogenesis factor.
- Administration of TNF-β induces metabolic acidosis, decreases the partial pressure of CO2, induces the synthesis of stress hormones such as epinephrine, norepinephrine, and glucagon, and alters glucose metabolism. (16)

Clinical Uses and Applications of TNF-β

The clinical applications of TNF-β are only in its initial stages

- Intrapleural administration of TNF-β significantly reduces liquid volumes in some metastasizing ascites tumors.
- The levels of TNF-β in the sera of patients with meningococcal septicemia correlate with morbidity and mortality.

TUMOR NECROSIS FACTOR (TNF) INHIBITORS

TNF promotes the inflammatory response, which in turn causes many of the clinical problems associated with autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis, crohn's disease, psoriasis and refractory asthma. These disorders are sometimes treated by using a TNF inhibitor. The important side effects that have been most extensively related to TNF-β blockers include: lymphoma, infections, congestive heart failure, demyelinating disease, a lupus-like syndrome, induction of auto-antibodies, injection site reactions and systemic side effects. (17)

This inhibition of TNF can be achieved with monoclonal antibodies such as:

- Infliximab (Remicade)
- Adalimumab (Humira)
- Certolizumab pegol (Cimzia) and
- Golimumab (Simponi), or with
- Etanercept (Enbrel) - a circulating receptor fusion protein.

While most clinically useful TNF inhibitors are monoclonal antibodies, some are simple molecules such as xanthine derivatives (18) (e.g. Pentoxifylline) (19) and Bupropion. (20)
The following conditions are known to be treated using TNF inhibitors:

i) *Crohn's Disease*, a gastrointestinal (GI) tract condition in which the small intestines and colon become inflamed.
ii) *Ankylosing Spondylitis*, also known as Bechterew's disease or syndrome, causes inflammatory arthritis in the spine as well as in sacroiliac joints and is considered extremely painful.
iii) *Rheumatoid Arthritis,* systemic inflammatory disorder principally attacking synovial joints.
iv) *Psoriatic Arthritis*, a disease that causes the skin and the joints to become inflamed. (21)

Side Effects of TNF Inhibition
TNF Inhibitors have a number of known side effects, mainly related to their immunosuppressant activity. Since TNF is an important cytokine when fighting against tuberculosis, these drugs can reactivate a latent tuberculosis infection. (22)

1) Tuberculosis
In patients with latent Mycobacterium tuberculosis infection, active tuberculosis (TB) may develop soon after the initiation of treatment with Infliximab. Before prescribing the drug, physicians should screen patients for latent TB infection or disease. (23)

2) Fungal infections
The U.S. Food and Drug Administration (FDA) issued a warning on September 4, 2008, that patients on TNF inhibitors are at increased risk of opportunistic fungal infections, such as pulmonary and disseminated histoplasmosis, coccidioidomycosis, and bastomycosis. (24)

Other side effects:

- Infection site reactions may occur although they are mild and decrease with repeated doses (including skin infections).
- Infections in addition to histoplasmosis.
- Malignancy.
- Immunogenecity. (21)

NATURAL COMPOUNDS HAVING TNF INHIBITORY ACTIVITY

TNF or the effects of TNF are also inhibited by a number of natural compounds, including curcumin (a compound present in turmeric) and catechins (in green tea).

Curcumin: Curcumin (*Curcuma longa)* markedly reduces acute and chronic skin toxicity and significantly decreases mRNA expression of early responding cytokines (IL-1 IL-6, IL-18, TNF-α, and lymphotoxin-β) and the fibrogenic cytokine, TGF-β, in cutaneous tissues. It has a protective effect on radiation-induced cutaneous damage and has been

shown to possess anti-inflammatory properties. Curcumin also prevents morphologic alterations in macrophages induced by endotoxin.The protective effect of curcumin makes it or its analogues strong candidates as a novel therapy for sepsis. The beneficial effect of curcumin appears to be mediated by up-regulation of nuclear receptor PPAR-γ. (25,26)

Green tea: Green tea (*Camellia* sinensis) catechins possess antibiotic properties due to their role in disrupting a specific stage of the bacterial DNA replication process. They also prevent vascular inflammation that plays a critical role in the progression of atherosclerotic lesions. (27)

THERAPEUTIC APPLICATIONS OF TUMOR NECROSIS FACTOR

Tumor necrosis factor in general has various therapeutic applications and finds an important role in:

1) Psoriasis. (28)
2) Rheumatoid arthritis and Ankylosing Spondylitis. (29)
4) Autosomal dominant polycystic kidney disease. (30)
5) Coronary heart disease. (31)
6) Obesity. (32)
7) Hyperandrogenism. (33)
8) Septic shock. (34)
9) Cerebral malaria. (35)
10) Alopecia areata. (36)
11) Osteoporosis and osteopenia. (37)
12) Asthma. (38)
13) Inflammatory bowel diseases. (39)
14) Hepatitis B. (40)
15) Cystic fibrosis. (41)
16) HLA-B27-associated uveitis. (42)
17) Insulin resistance and diabetes. (43)
18) Vascular dementia. (44)
19) Skin diseases. (45)

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