Chapter 3

Targeting TNF for Treatment of Cancer and Autoimmunity

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Abstract

Tumor necrosis factor-α (TNF-α) was first isolated two decades ago as a macrophage-produced protein that can effectively kill tumor cells. TNF-α is also an essential component of the immune system and is required for hematopoiesis, for protection from bacterial infection and for immune cell-mediated cytotoxicity. Extensive research, however, has revealed that TNF-α is one of the major players in tumor initiation, proliferation, invasion, angiogenesis and metastasis. The proinflammatory activities link TNF-α with a wide variety of autoimmune diseases, including psoriasis, inflammatory bowel disease, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, multiple sclerosis, diabetes and ankylosing spondylitis. Systemic inhibitors of TNF such as etanercept (Enbrel) (a soluble TNF receptor) and infliximab (Remicade) and adalimumab (Humira) (anti-TNF antibodies) have been approved for the treatment inflammatory bowel disease, psoriasis and rheumatoid arthritis. These drugs, however, exhibit severe side effects and are expensive. Hence orally active blockers of TNF-α that are safe, efficacious and inexpensive are urgently needed. Numerous products from fruits, vegetable and traditional medicinal plants have been described which can suppress TNF expression and TNF signaling but their clinical potential is yet uncertain.

Discovery of TNF

Tumor necrosis factor (TNF), an activity in the serum of endotoxin-injected animals, was first identified in 1944, rediscovered in the mid-1970s and chemically isolated from macrophage-conditioned medium as a cytokine that kills tumor cells in culture in 1984.[1,2] Two distinct factors were identified in macrophages and lymphocytes: TNF-α and TNF-β, respectively. The identification of their primary amino acid sequences led to the cloning of their genes and the availability of large amounts of pure cytokines for preclinical and clinical evaluation. Intravenous administration of TNF to cancer patients produced numerous toxic reactions including fever.[3] In animal studies, TNF-α has been shown to mediate endotoxin-mediated septic shock.[4] Several reports over the past years have indicated that dysregulation of TNF-α synthesis mediates a wide variety of autoimmune diseases and cancer.[2]

Signaling Mechanism(s) by TNF-α

TNF-α mediates its effects through two different receptors: TNF receptor I (also known as p55 or p60) and TNF receptor II (also known as p75 or p80). Whereas TNF receptor I is expressed

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on all cell types in the body, TNF receptor II is expressed selectively on endothelial cells and on cells of the immune system.[2-5] The cytoplasmic domain of the TNF receptor I has a death domain, which has been shown to sequentially recruit TNF receptor-associated death domain (TRADD), Fas-associated death domain (FADD) and FADD-like ICE (FLICE) (also called caspase-8) lead to caspase-3 activation, which in turn induces apoptosis by inducing degradation of multiple proteins.[6] TRADD also recruits TNF receptor-associated factor (TRAF2), which through receptor-interacting protein (RIP) activates IκBα kinase (IKK) leading to IκBα phosphorylation, ubiquitination and degradation, which finally leads to NF-κB activation. Through recruitment of TRAF2, TNF also activates various mitogen-activated protein kinases (MAPK), including the c-jun N-terminal kinases (JNK) p38 MAPK and p42/p44 MAPK. TRAF2 is also essential for the TNF-induced activation of AKT, another cell-survival signaling pathway. Thus TNFRI activates both apoptosis and cell survival signaling pathways simultaneously.[7-9]

Gene-deletion studies have shown that TNFR2 can also activate NF-κB, JNK, p38 MAPK and p42/p44 MAPK.[10] TNFR2 can also mediate TNF-induced apoptosis.[11] Because TNFR2 cannot recruit TRADD-FADD-FLICE, how TNFR2 mediates apoptosis is not understood. However, the true physiological role of TNF, its receptors and associated proteins has been explored through gene-deletion experiments. It was found that animals with homologous gene deletion are fully viable but are more susceptible to infection[12-24] (Table 1). Overall the deletion of TNF, its receptors and associated proteins indicates the critical role of this cytokine in protection from microorganisms, the formation of lymph nodes and the development of the immune system.

Role of TNF-α in Cancer

TNF-α, initially discovered as a result of its antitumor activity, has now been shown to mediate all steps involved in tumorigenesis, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis and metastasis[25] (Fig. 1). These are discussed in detail as follows.

TNF-α Can Induce Tumor Initiation and Promotion

A number of reports indicate that TNF-α induces tumor initiation and tumor promotion[5,26,27] Komori's group reported that human TNF-α is 1000 times more effective than the chemical tumor promoters okadaic acid and 12-O-tetradecanoylphorbol-13-acetate in inducing cancer. Once initiated with these chemical carcinogens and exposed for 2 weeks to TNF-α, BALB/3T3 cells underwent transformation and yielded tumors in nude mice.[28] The essential role of TNF-α in tumor promotion has also been demonstrated using TNF-α-deficient mice. Specifically, okadaic acid did not show any tumor-promoting activity in $TNF^{-/-}$ mice after up to 19 weeks of tumor promotion, whereas okadaic acid induced strong tumor-promoting activity in $TNF^{+/+}$ mice. Tumor development in TPA-treated $TNF^{-/-}$ mice was delayed and both the average number of tumors per mouse and the tumor size were dramatically reduced compared with results for $TNF^{+/+}$ CD-1 mice.[29] Similarly, in a model of chemically induced liver cancer, TNF-α production by hepatocytes was implicated in tumor development.[30] All these reports establish that TNF-α plays a critical role in tumor promotion.

Tumor Cells Produce TNF-α and Mediate Proliferation

TNF-α is also produced by a wide variety of tumor cells, including B-cell lymphoma,[31,32] cutaneous T-cell lymphoma,[33] megakaryoblastic leukemia,[34] adult T-cell leukemia,[35] CLL,[36] ALL,[37] breast carcinoma,[38] lung carcinoma,[39] pancreatic cancer,[40] ovarian carcinoma,[41] cervical epithelial cancer,[42] glioblastoma[43] and neuroblastoma.[44] In most of these cells, TNF-α acts as an autocrine growth factor; however; in some cell types TNF-α induces the expression of other growth factors that mediate proliferation of tumors. For instance, in cervical cells TNF-α induces amphiregulin, which induces the proliferation of cells,[42] whereas in pancreatic cells TNF-α induces the expression of epidermal growth factor receptor (EGFR) and transforming growth factor (TGF-α), which mediate proliferation.[40]

Table 1. Phenotype of mice with gene deletion for TNF, TNF receptor and receptor-associated proteins

Gene	Phenotype	Ref.
TNF	• Homozygous mutants viable • Readily succumb to *Listeria monocytogenes* infection • Show reduced contact hypersensitivity responses • Resistant to lipopolysaccharide toxicity • Lack splenic primary B-cell follicle follicular dendritic cell network • Exhibit resistance to skin carcinogenesis	12-14
TNFR1	• Resistant to low levels of lipopolysaccharide • Increased susceptibility to *Listeria monocytogenes* infection	15
TNFR2	• Resistant to low levels of lipopolysaccharide • Impaired T-cell development • Reduced cytotoxic T-lymphocyte proliferation • Increased resistance to TNF-induced necrotic cell death	16
TRAF1	• Exhibit stronger proliferation than wild-type T-cell to anti-CD3 • Respond to TNF-induced NF-κB and AP-1 signaling pathways • Skin hypersensitive to TNF-induced necrosis	17
TRAF2	• Defective Th-dependent antibody response • CD40-mediated proliferation and NF-κB activation • Thymus and spleen atrophied and B-cell precursors depleted • Thymocytes and hematopoietic progenitors sensitive to TNF-induced apoptosis • Serum TNF levels elevated • Reduced TNF-mediated JNK/SAPK activation Mild effect on NF-κB activation	18, 19
RIP1	• Appear normal at birth but fail to thrive • Die at 1-3 days of age • Extensive apoptosis in lymphoid and adipose tissue • $RIP^{-/-}$ cells highly sensitive to TNFα-induced cell death • No NF-κB activation	20
FADD	• Do not survive beyond day 11.5 of embryogenesis • Cardiac failure and abdominal hemorrhage • Chimeric embryos showing a high contribution of FADD null mutantcells to the heart reproduce the phenotype of $FADD^{-/-}$ mutants • Activates rearrangement of the immunoglobulin and TCR genes • Fas-induced apoptosis completely blocked • Fas-mediated activation-induced proliferation impaired	21, 22
Caspase-8	• Embryos exhibit impaired heart muscle development • Congested accumulation of erythrocytes in embryos • TNF receptors, Fas/Apo1 and DR3 fail to induce cell death	23
IKKβ	• Die at mid-gestation from uncontrolled liver apoptosis • IKKβ-deficientcells lack activation of IKK and NF-κB in response to TNF-α or IL-1β	24

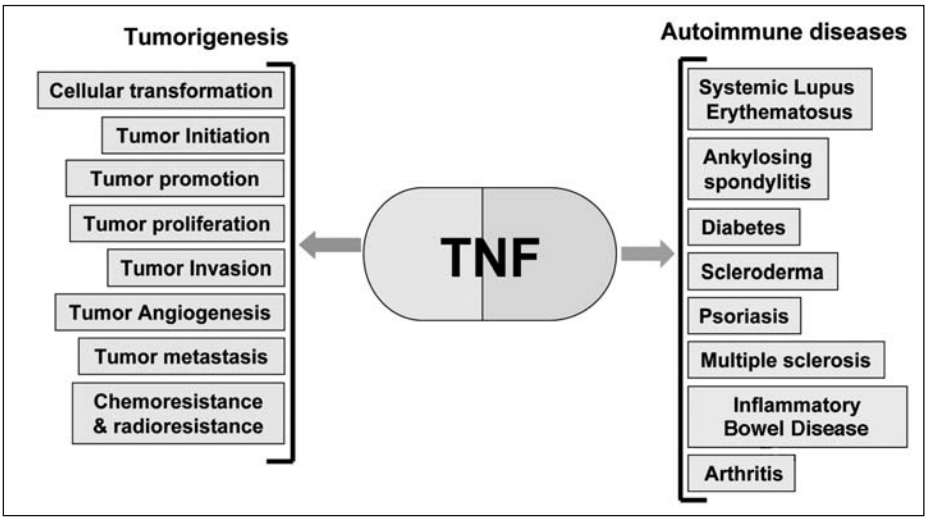

Figure 1. Pro-inflammatory effects of TNF are involved in tumorigenesis and in autoimmune diseases.

TNF-α Can Induce Invasion and Angiogenesis of Tumor Cells

That TNF-α can induce invasion and angiogenesis of tumor cells is well documented. TNF-α has been shown to confer an invasive, transformed phenotype on mammary epithelial cells.[38] TNF-α has been reported to induce angiogenic factor upregulation in malignant glioma cells.[45] This upregulation in turn promotes angiogenesis and tumor progression. TNF-α also stimulates epithelial tumor cell motility, which is a critical function in embryonic development, tissue repair and tumor invasion.[46] TNF-α has been even reported to mediate macrophage-induced angiogenesis.[47]

Role of TNF-α in Tumor Metastasis

TNF-α also plays a role in the metastasis of cancer cells. In a model of experimental lung metastasis of colon adenocarcinoma, injection of LPS into mice enhanced the development of metastatic lesions. The increased metastasis was dependent on TNF-α production by host hematopoietic cells. This TNF-α activated NF-κB in the tumor cells, increasing their proliferation and survival.[48] Moreover, endogenous and exogenous TNF-α administration enhanced metastasis in an experimental fibrosarcoma metastasis model.[49] Mice injected with fibrosarcoma cells showed enhanced metastasis to the lungs in the presence of exogenous TNF. Neutralization of endogenous tumor-induced TNF led to a significant decrease of the number of pulmonary metastases. An essential role of TNFR p55 has been found in liver metastases following intrasplenic administration of colon 26 cells.[50] Malik et al described found that overexpression of TNF-α conferred invasive properties on xenograft tumors.[51] Neutralization of endogenous TNF-α reversed the hepatic metastases and prolonged survival in mouse models.[52]

Role of TNF-α in the Immune System

TNF-α is a critical component of effective immune surveillance and is required for proper proliferation and function of natural killer cells (NK-cells), T-cells, B-cells, macrophages and dendritic cells.[5] TNF-α can influence inflammation and innate immunity, lymphoid organization and activation of APCs and can provide direct signals to T-cells.[2,53-55] TNFR2 can augment T-cell proliferation and thus may also provide a costimulatory signal for T-cells.[56] Mice strains in which the TNF-α gene or its p55 receptor has been deleted (TNF-KO or TNFR1-KO mice) have severe defects in lymph node follicle and germinal center formation.[57-59] TNF-α acting through TNF

receptor p55 is involved in the development/maturation of dendritic cells (DCs) in bone marrow progenitor cultures.[60] Moreover, the microenvironment in peripheral lymphoid organs is associated with TNF-α signaling and chemokine production is critical for recruitment efficiency of DCs.[60] Follicular DCs are specialized mesenchymal cells that collect antigens in draining lymph nodes, interact with clonally expanding B-cells and form networks in the follicle under the influence of TNF-α and TNF-β.[53]

TNFR1 is a costimulator of T-cell activation and is expressed by activated T-cells. The initiation of an immune response by dendritic cells originating in epithelial barriers and stimulating naive T-cells in draining lymph nodes involves active involvement of TNF/TNFR1. Moreover, TNF-α regulates the expansion and survival of $CD4^+$ and $CD8^+$ T-cells.[53,54] T-cell-derived TNF-α is important for protection against high bacterial load, whereas mastcell-derived TNF-α is a critical and early component of the allergic response.[61]

TNF-α also plays a central role in initiating the inflammatory reactions of the innate immune system. Bacterial pathogens and several other proinflammatory and environmental stimuli induce TNF-α and NF-κB signaling cascade via Toll-like receptors and also enhance its translational efficiency.[62] Early production of TNF-α is prominent in the subsequent initiation of a highly complex biological cascade involving chemokines, cytokines and endothelial adhesions that recruits and activates neutrophils, macrophages and lymphocytes at the sites of infections. Release of preformed TNF-α acts as a positive autocrine feedback signal to activate NF-κB and to induce further TNF-α and other cytokines such as granulocte-monocyte colony-stimulating factor (GM-CSF) and IL-8.[61] Thus TNF-α exerts a global regulatory effect on the immune system.

Role of TNF-α in Autoimmune Diseases

Dysregulation of TNF-α has been implicated in a wide variety of autoimmune diseases, including rheumatoid arthritis, Crohn's disease, multiple sclerosis, psoriasis, scleroderma, systemic lupus erythromatosus, ankylosing spondylitis and diabetes (Fig. 1). How TNF-α mediates disease-causing effects is incompletely understood. The induction of proinflammatory genes by TNF-α has been linked to most diseases. The proinflammatory effects of TNF-α are primarily due to its ability to activate NF-κB.[63] Almost all cell types, when exposed to TNF-α, activate NF-κB, leading to the expression of inflammatory genes. The role of TNF-α in some of the autoimmune diseases is discussed in detail below.

Psoriasis

Psoriasis is a chronic inflammatory disease of the skin, affecting 2-3% of the world's population. Histopathologically, psoriasis is characterized by hyperproliferation of epidermal keratinocytes and hyperkeratosis, as well as infiltration of immunocytes along with angiogenesis.[64] T-cells play a major role in the initiation of psoriatic lesions. Activated T-cells in the region of the dermal epidermal junction promote the hyperplastic proliferative response through increased production of Th1 cytokines, among which TNF-α is the major player.[65] In psoriatic lesions, levels of TNF-α-induced genes, such as IL-1β, IL-8 and IL-6, are greatly increased.[66-68] Furthermore, in psoriatic plaques, there is a significant upregulation of activated phosphorylated NF-κB compared with normal epidermis and uninvolved epidermis from psoriasis patients.[69] TNF blockers have been shown to reverse the epidermal hyperplasia and cutaneous inflammation characteristic of psoriatic plaques.[70] All these findings together suggest a major role for TNF-α in both initiation and progression of psoriasis.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is characterized by a chronic relapsing inflammation of the gastrointestinal tract and is divided into two primary forms: Crohn's disease and ulcerative colitis.[71] IBD is associated with the activation of local intestinal and systemic immune responses and is caused by the loss of tolerance against intestinal antigens.[72] TNF-α levels are elevated in the serum, mucosa and stool of IBD patients and $TNF^{-/-}$ mice show a marked reduction in chemically induced intestinal inflammation.[73-76] Increased nuclear translocation of NF-κB has also been shown

in lamina propria mononuclear cells derived from IBD patients.[77] Hence TNF-α is considered to be an attractive target for the treatment of IBD and several antiTNF reagents have been developed, but most of them have not proven safe and efficacious in the treatment of IBD.

Arthritis

As a proinflammatory cytokine, TNF-α has perhaps the most dominant role in the etiology of rheumatoid arthritis.[78] Patients with rheumatoid arthritis have high concentrations of TNF-α in the synovial fluid and at the cartilage-pannus junction, which leads to the erosion of bone.[79,80] In cultures of synovial cells from patients with rheumatoid arthritis, blocking TNF-α with antibodies significantly reduced the production of IL-1β, IL-6, IL-8 and GM-CSF.[81] Hence, the inhibition of TNF-α has a more global effect on inflammation than the suppression of other cytokines present in high concentrations in synovial fluids, such as IL-1β. The results of studies in animals provide further evidence of the importance of TNF-α in rheumatoid arthritis. In transgenic mice that expressed a deregulated human TNF-α gene, an inflammatory and destructive polyarthritis similar to rheumatoid arthritis spontaneously developed.[82] AntiTNF-α therapies are being used for the treatment of rheumatoid arthritis, but these agents are associated with side effects, some of them quite serious.[83] Hence novel agents are needed for the management of rheumatoid arthritis.

Systemic Sclerosis (Scleroderma)

Systemic sclerosis (scleroderma) is a generalized connective tissue disorder, characterized by a wide spectrum of microvascular and immunological abnormalities, leading to progressive thickening and fibrosis of the skin and other visceral organs, such as the lungs, gastrointestinal tract, heart and kidneys.[84,85] Compelling evidence indicates that the increased production of TNF-α is involved in the pathogenesis of scleroderma.[86] Patients with systemic sclerosis exhibit a systemic and local rise in TNF-α levels that leads to pulmonary fibrosis.[87] The serum levels of TNFR1 are directly correlated to the severity of the disease.[88] TNF-α gene polymorphism is also associated with scleroderma.[89] Thus dysregulation of TNF-α plays a critical role in the development of systemic sclerosis in normal human subjects.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease characterized by the breakdown of self-tolerance, B-cell hyperactivity, autoantibody production, aberrant formation of immune complexes and inflammation of multiple organs.[90] The TNF-α level is increased and seems to be bioactive in the serum of patients with active SLE. The levels of TNF-α have been shown to correlate with SLE disease activity.[91,92] Various antiTNF-α agents are currently being used for the treatment of SLE.

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is an autoimmune disease characterized by prominent inflammation of the spinal joints and adjacent structures leading to progressive bony fusion of the spine.[93] Pathophysiologically, TNF-α appears to play a role in promoting the inflammatory pattern associated with AS. Increased TNF-α protein is found in the sacroiliac joints[94] and peripheral synovium[95,96] as well as the serum[97,98] of patients with active AS. While disease activity cannot be predicted from levels of TNF-α, blockade of this protein has been shown to have benefits in animal models and human studies of AS. Considering the critical role of TNF-α in the pathogenesis of AS, the molecules targeted at blocking the effects of TNF-α are likely to play a crucial role in the management of this disease.

Diabetes Mellitus

Autoimmune diabetes, or insulin-dependent diabetes mellitus (IDDM), is characterized by selective destruction of insulin-producing cells.[99] The role of TNF-α in the pathogenesis of autoimmune diabetes has received increasing attention recently.[100] It was shown that TNF-α in combination with IFN-γ could induce the aberrant expression of class II major histocompatibility complex

(MHC) molecules on pancreatic beta cells, suggesting a role for these cytokines in the induction of the autoimmune process in diabetes.[101] A different group of investigators has suggested that IL-1β is toxic to pancreatic beta cells and that TNF-α significantly enhances this toxicity.[102] Transgenic mice, expressing constitutively active IKK-β, a kinase required for activation of NF-κB, exhibited type 2 diabetes phenotype and increased hepatic production of TNF-α. Hepatic expression of the IκBα super repressor reversed this diabetic phenotype in transgenic mice as well as wild-type mice fed a high-fat diet.[103] These findings indicate that lipid accumulation in the liver leads to subacute hepatic 'inflammation' through NF-κB activation and downstream cytokine production. This causes insulin resistance both locally in liver and systemically. Thus novel blockers of TNF-α have significant implications for future new therapeutic strategies for insulin-dependent diabetes mellitus.

Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system characterized by localized areas of demyelination.[104] TNF-α plays an important role in the pathogenesis of MS and its animal model, experimental autoimmune encephalomyelitis.[105,106] TNF-α has been detected in MS plaques[107,108] and circulating levels of TNF-α and its receptor have been found in cerebro-spinal fluid of MS patients.[109,110] All these findings support an enormous role for TNF-α inhibitors in the treatment of multiple sclerosis.

TNF Inhibitors

On the basis of the above descriptions, TNF blockers have tremendous potential for the treatment of various cancers and autoimmune diseases. Several classes of TNF-α inhibitors are available and these are discussed below.

TNF Antibodies

The best studied of the monoclonal TNF-α antibodies is infliximab (Remicade), originally referred to as cA2. Infliximab binds with high specificity and affinity to free and membrane-bound TNF-α, which is expressed at the cell surface by activated T-cells and macrophages.[111] Adalimumab (Humira) is a human monoclonal IgG_1 antibody containing only human peptide sequences. It binds with high specificity and affinity to soluble and membrane-bound TNF-α and blocks its interaction with the p55 and p75 cell surface TNF receptors, thereby neutralizing the biological activities of this cytokine.[112] However, these antibodies have demonstrated several potentially serious adverse effects that include greater predisposition towards infection, congestive heart failure, neurologic changes (e.g., demyelination), lymphomas, re-exacerbation of latent tuberculosis and problems related to autoimmunity, for example lupus-like syndrome.[113]

Soluble TNF Receptors

In the second approach to TNF-α inhibition, soluble TNF receptors have been engineered as fusion proteins in which the extracellular ligand-binding portion of TNFRI or TNFR2 is coupled to a human immunoglobulin-like molecule. Etanercept (Enbrel) is a recombinant human fusion protein that consists of two soluble p75 TNF receptors and the F_c portion of human IgG_1.[114] Etanercept possesses a dimeric structure with high affinity to TNF-α and the linkage to the F_c portion of human IgG produces a longer half-life. Etanercept is better at neutralizing TNF-α than is the monomeric soluble p75 receptor. The various side effects observed include lymphomas, re-exacerbation of latent tuberculosis and problems related to autoimmunity.[113] Recent studies indicate that administration of TNF-α inhibitors can even lead to psoriasis[115] and contribute to the severity of the disease in paracoccidioidomycosis.[116]

Besides p75, TNF has been shown to bind to p55 receptor with an affinity either equal or even greater than p75.[117] Although soluble p75 receptors clearly can sequester TNF, very little is known about the ability of the soluble form of the p55 receptor to sequester TNF in vivo.

Inhibitors of TNF Expression

Several compounds that can inhibit both TNF-α expression and synthesis are also available. These include thalidomide ([+]-alpha-phthalimidoglutarimide), which is currently being used for treatment of multiple myeloma[118,119] and pentoxifylline, used to treat leg pain caused by poor blood circulation.[120] Thus these agents may be useful for the treatment of various cancers and autoimmune diseases mediated by TNF.

Inhibitors of TNF Oligomerization

Some inhibitors that can suppress oligomerization of TNF are also known. Steed and coworkers[121] designed a novel dominant-negative variant TNF protein that rapidly forms heterotrimers with native TNF to give complexes that neither bind to nor stimulate signaling through TNF receptors and thus inactivate TNF by sequestration. He et al[122] identified another small-molecule inhibitor that promotes subunit disassembly of trimeric TNF. This compound inhibited TNF activity in biochemical and cell-based assays, with median inhibitory concentrations of 22 and 4.6 micromolar, respectively. Formation of an intermediate complex between the compound and the intact trimer resulted in a 600-fold accelerated subunit dissociation rate that led to trimer dissociation.

Inhibitors of TNF-α-Induced Signaling Pathways

TNF-α activates cell survival signaling pathways, i.e., NF-κB, Akt and MAPK pathways, as well as apoptotic pathways such as JNK, p38 and AP-1. Hence, inhibitors that target these pathways also have potential against various proinflammatory conditions mediated by TNF-α. For example, TNF-α activates NF-κB, which in turn regulates TNF-α production. Hence various NF-κB blockers (both synthetic and natural) are currently available on the market and effective against a wide variety of inflammatory conditions.

Natural Products as Inhibitors of TNF

Numerous plant-derived products have been identified that can suppress TNF-α expression from macrophages activated by numerous inflammatory stimuli (129-165, see Table 2). These include curcumin, resveratrol, emodin, silymarin and others. Thus these products are likely to be useful for the treatment of cancer and autoimmune diseases mediated by TNF.

Table 2. A list of natural products that inhibit the expression of TNF

- 1′-acetoxychavicol acetate[123]
- 1′-acetoxyeugenol acetate[124]
- *Allium sativum*[125]
- *Aloe vera*[126]
- *Aloe barbadensis*[127]
- *Asparagus cochinchinensis*[128]
- Bisdemethoxycurcumin[129]
- Butein[130]
- Cardamomin[131]
- Curcumin[132, 133]
- Diphenyl dimethyl bicarboxylate[134]
- Emodin inhibits IL-1β and IL-6[135]
- Epigallocatechin gallate[136]
- F022[137]
- Ginkgolide B[138, 139]
- 2′-Hydroxychalcone[140, 141]
- Hypoestoxide[142]
- *Lonicera japonica*[143]
- Neolignans and lignans[144]
- Patridoids I, II and IIA[145]
- Phthalide lactone[146]
- Phloroglucinol derivatives[147]
- Platycodin D and D3[148]
- *Phlebodium decumanum*[149]
- *Phyllanthus amarus*[150]
- Resveratrol[151]
- 14,15-Secopregnanederivatives argelosides[152]
- Silymarin[153]
- *Tanacetum microphyllum*[154]
- *Taraxacum officinale*[155]
- Δ^9-Tetrahydrocannabinoid[156]
- *Theobroma cacao*[157]
- *Uncaria guianensis*[158]
- *Zostera japonica*[159]

Conclusion

TNF clearly plays a major role in cancer and in autoimmune diseases. Because TNF is also needed for the proper functioning of the immune system, complete suppression of TNF over a long period is likely to prove harmful. The potential of TNF inhibitors in the treatment of autoimmune diseases as employed currently is just "the tip of the iceberg." Any chronic inflammatory condition, linked to majority of the inflammatory diseases, could be a potential target for antiTNF therapy. Thus the development of inhibitors that are orally active, safe and inexpensive would have major potential. Because of long-term safety and cost, nutraceuticals derived from fruits and vegetables, that can suppress TNF expression and TNF signaling, should be explored clinically for efficacy.

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