Tumor Necrosis Factor and Anti-Tumor Necrosis Factor Therapies

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ABSTRACT. Tumor necrosis factor (TNF) plays a crucial role in the pathogenesis of immune-mediated inflammatory diseases (IMID). As a result, the inhibition of TNF is an important therapeutic avenue in the treatment of these pathophysiologically diverse disease states. This section discusses TNF, its receptors, and its role in immunoregulation and inflammation, as well as the currently available anti-TNF-based therapies. (J Rheumatol 2010;37 Suppl 85:27–39; doi:10.3899/jrheum.091463)

Key Indexing Terms:
TUMOR NECROSIS FACTOR BIOLOGIC THERAPIES
IMMUNE-MEDIATED INFLAMMATORY DISEASES

Tumor necrosis factor (TNF) plays a pivotal role in various immune and inflammatory processes, including cellular activation, survival and proliferation, as well as cell death by necrosis and apoptosis. The cellular source of TNF depends on the nature of the stimulus. TNF is produced primarily by cells of hematopoietic origin, including myeloid lineage such as monocytes and macrophages, when stimulated by innate sensors, such as the Toll-like receptor (TLR) system. T and B lymphocytes can also produce TNF in response to antigenic stimulation.

Dysregulation of inflammatory pathways driven by cytokines such as TNF is believed to be a common underlying mechanism leading to immune-mediated inflammatory diseases (IMID). This is supported by the finding that TNF is upregulated in the majority of IMID (Table 1)[1], despite the very different clinical manifestations of these disorders. It is also important to note that similar cytokine dysregulation can cause an array of pathologies in different organ systems, depending on when, where, why, and how the dysregulation occurs. The development of TNF inhibitors has clinically demonstrated the dominant role played by TNF in IMID such as rheumatoid arthritis (RA), psoriasis (Ps), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and Crohn's disease (CD), and significantly improved outcomes of patients affected by these disorders.

However, anti-TNF therapies are not without disadvantages. For example, there are considerable differences in the response rates among different patients within a given IMID. While some patients respond quickly, others may take considerably longer, and some may not respond to the initial anti-TNF agent at all. Further, some patients may lose their response over time. In addition, there are considerable differences in the efficacy of anti-TNF therapies in different IMID. For example, in contrast to monoclonal antibodies (adalimumab and infliximab), the decoy TNF receptor (etanercept) has not proven effective in treating inflammatory bowel disease (IBD) or uveitis.

This article provides an overview of the biology of TNF and related family members in the context of the potential mechanisms of action of TNF inhibitors in a variety of IMID. Differences between currently available agents are addressed with regard to their therapeutic efficacy.

ROLE OF TNF AND ITS RECEPTORS IN INFLAMMATION AND IMMUNOREGULATION

TNF Superfamily

TNF is a member of a family of structurally related cytokines that signal through specific cell-surface receptors that also form a structurally related family of proteins (Figure 1)[2]. The TNF superfamily consists of more than 35 specific ligand-receptor pairs that play pivotal roles in many biological processes in mammalian cells, such as host defense, inflammation, apoptosis, autoimmunity, and development and organogenesis of the immune, ectodermal and nervous systems[3]. The genes encoding lymphotoxin α (LTα), LTß, and TNF reside in tightly linked loci within the major histocompatibility complex (MHC) on chromosome (Chr) 6 in humans (Chr 17 in the mouse) (Figure 1). Their receptors are linked on Chr 12 (mouse Chr 6). Three other

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Dr. Keystone has acted as advertising board member and speaker for, and research funding recipient from, Abbott, Schering Plough, UCB, Hoffman-LaRoche, Amgen, Centocor, Celgene, Lux Biosciences, Allergan, Wyeth, and Bristol-Myers Squibb; advertising board for Genentech and UCB; and research funding recipient from Novartis. Dr. Ware has acted as a speaker for Abbott and consultant for Amgen.

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Table 1. Overexpression and underexpression of specific cytokines in immune-mediated inflammatory diseases (IMID). From Williams and Meyers, Am J Manag Care 2002;8 Suppl 21:S664–S681; with permission[1].

Condition	Cytokines Overexpressed	Cytokines Underexpressed
Crohn's disease	TNF, IL-1, IL-2, IL-6, IL-8, IL-12, IFN-γ	IL-3
Psoriatic arthritis	TNF, IL-1, IL-6, IL-8, IFN-γ	
Psoriasis	TNF	
Ankylosing spondylitis	TNF, IL-10	IFN-γ, IL-2
Rheumatoid arthritis	TNF, IL-1, IL-6	
Ulcerative colitis	TNF, IL-1, IL-5, IL-6, IL-8	IL-3

TNF: tumor necrosis factor; IL: interleukin; IFN: interferon.

MHC paralogous genomic regions contain the related family members (Chr 19 LIGHT, CD27L, 41BBL; Chr 1 FasL, GITRL, Ox40L; Chr 9 CD30, TL1A). The receptors for these ligands (except FasL) are linked on Chr 1p36[4].

Basic Structure of the TNF Molecule

The TNF-related ligands are type II (intracellular N-terminus) transmembrane proteins containing a "TNF homology domain" at the extracellular C terminus (Figure 2)[5,6]. TNF is initially synthesized as a monomer that folds into a ß-sheet sandwich and assembles into a functional trimer. Thus, each TNF ligand has 3 receptor binding sites, formed as a groove between adjacent subunits. The trimeric structure promotes efficient clustering of TNF's specific receptors, which in turn activate signaling pathways and cellular responses. The trimeric protein is made as a 27-kDa uncleaved, type 2 transmembrane form, which is processed into a 17-kDa secreted form at the cell surface. The transmembrane form (tmTNF) is cleaved to the soluble form (sTNF) by TNF-α convertase (TACE), a member of the ADAM disintegrin and metalloproteinase family[7]. Although both soluble and membrane forms of the TNF ligands are biologically active, the transmembrane form is about 1000 times more potent than a soluble form on a per-mole basis[8].

Regulation of TNF Biosynthesis

Many different immune and nonimmune cell types can produce TNF, including macrophages, T cells, mast cells, granulocytes, natural killer (NK) cells, and nonhematopoietic

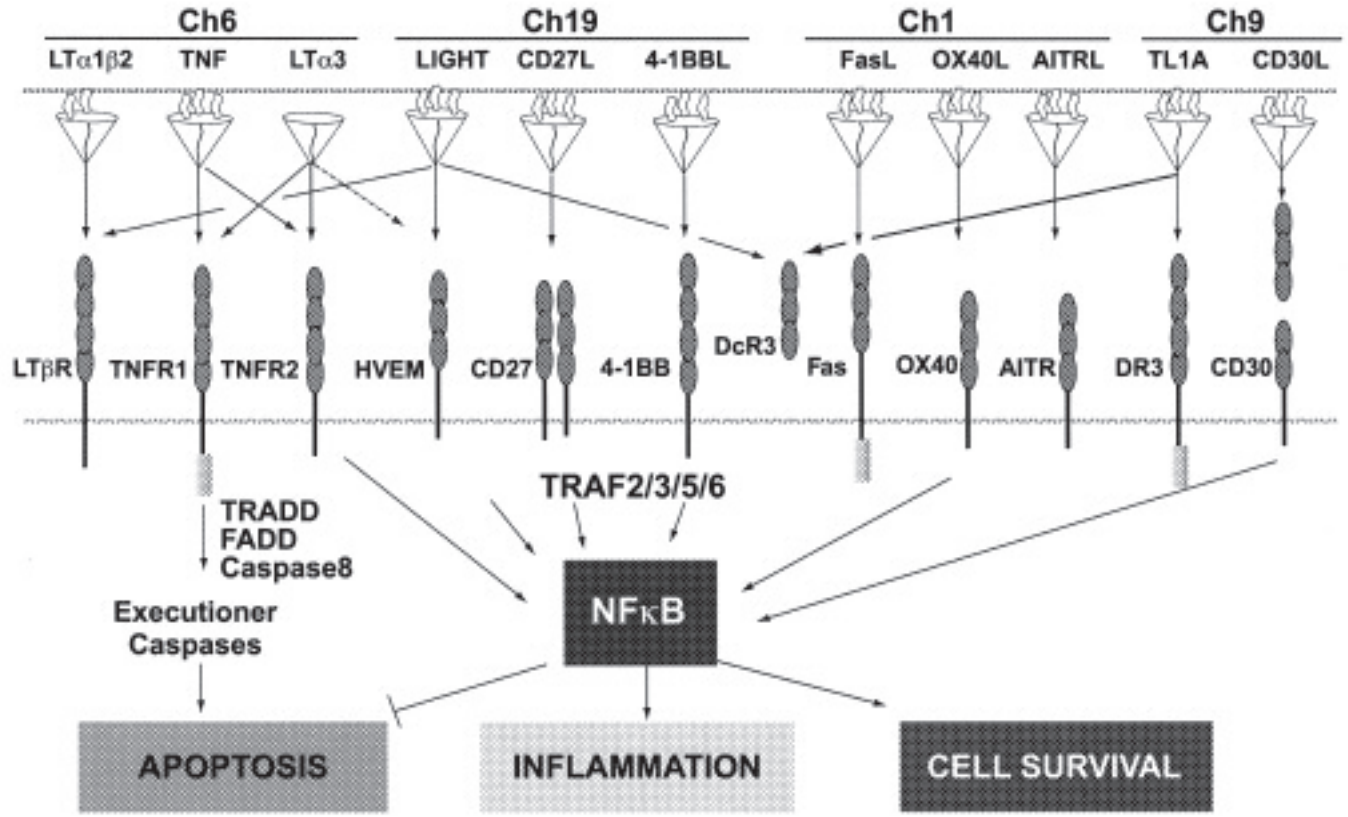

Figure 1. The TNF superfamily: MHC paralogs. TNF and related ligands encoded in the MHC (chromosome 6) and paralogous regions on chromosomes 1, 9, and 19, and their receptors. Arrows indicate interactions with receptor, where known. MHC: major histocompatibility complex; Ch: chromosome; LT: lymphotoxin; L: ligand; AITR: activation-inducible TNF receptor; TL1A: TNF-like cytokine; HVEM: herpes virus entry mediator; TRADD: TNF receptor-associated death domain; FADD: Fas-associated death domain; TRAF: TNF receptor-associated factor; NF-κB: nuclear factor-κB. From Ware CF, Cytokine Growth Factor Rev 2003;14:181-4; with permission from Elsevier[2].

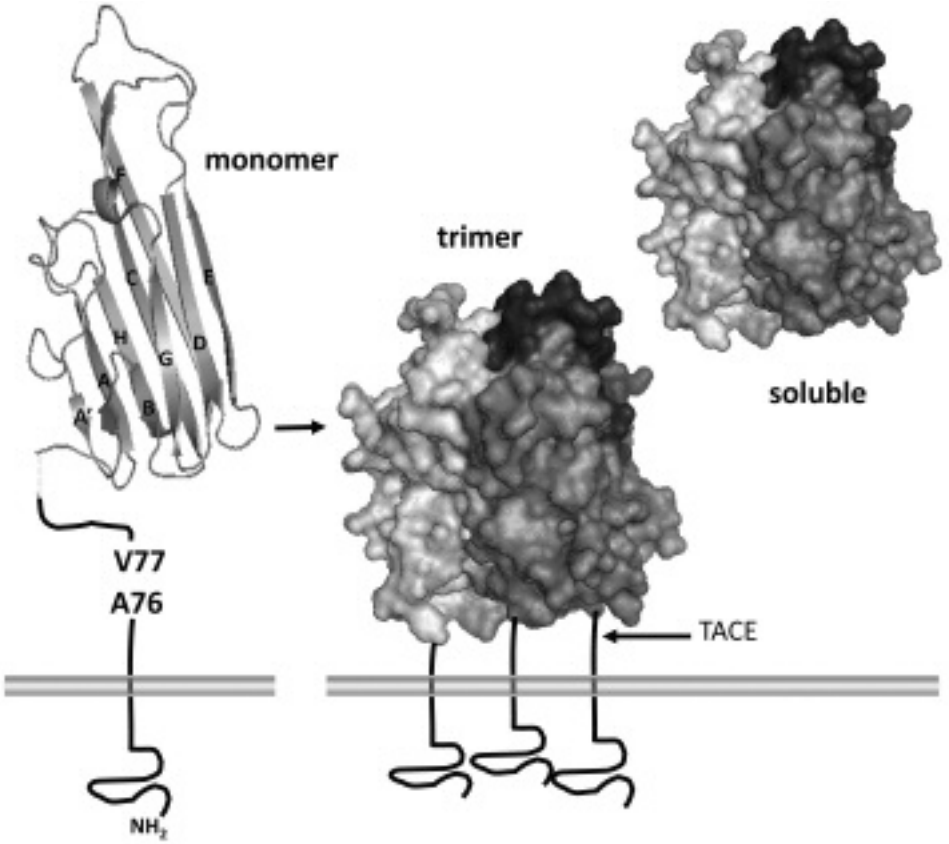

Figure 2. Basic structure of the TNF molecule. The TNF-related ligands are type II (intracellular N-terminus) transmembrane proteins containing a "TNF homology domain" (THD) at the extracellular C terminus. TNF is initially synthesized as a monomer that folds into a ß-sheet sandwich and assembles into a functional trimer. The membrane-bound form (tmTNF) is cleaved to the soluble form (sTNF) by TNF-α convertase (TACE). From Ware CF, TNF-related cytokines in immunity. In: Paul WE, editor. Fundamental immunology. 6th ed.; with permission from Wolters Kluwer/Lippincott Williams & Wilkins[6].

cells, such as fibroblasts, neurons, keratinocytes, and smooth-muscle cells. The ability to produce TNF depends on the nature of the stimulus. T cells produce TNF in response to antigen stimulation, whereas activation of innate sensors, such as the TLR, induces TNF production in macrophages and many other cell types. TNF biosynthesis and bioavailability are controlled at the transcriptional level and by control of protein accessibility (Figure 3)[6].

Regulation of TNF biosynthesis at the transcriptional level. The first point of regulation of TNF is at the transcriptional stage by adenosine and uridine (AU)-rich elements (ARE) in the 3' mRNA. ARE were identified as determinants of mRNA instability more than 2 decades ago[9,10], and it is presently clear that ARE are responsible for regulating the decay of many mRNA[11,12]. The core sequence of ARE is a nucleotide pentamer containing the AUUUA motif[11]. The ARE interact with sequence-specific, RNA-binding proteins, which serve to coordinate instability or enhanced stability, depending on the circumstance[13]. A significant body of evidence demonstrates the importance of mRNA stability as a regulator of the inflammatory response. This is also documented for the mRNA encoding TNF[14]. TNF mRNA contains a clustered AUUUA pentamer motif that confers instability, sensitivity to stimulus-driven stabilization, and stimulus-sensitive control of translational efficiency. Mice expressing a TNF gene in which the ARE motif has been deleted exhibit a systemic inflammatory syndrome, which is characterized by elevated TNF expression, widespread inflammatory cell infiltrates, IBD, and polyarthritis[14].

Regulation of TNF at the receptor level. The second point of regulation of TNF bioavailability is at the receptor level. TACE regulates TNF biosynthesis at the receptor level by cleaving membrane-bound TNF receptor (TNFR) to form soluble receptors capable of binding TNF[15,16]. This process is referred to as receptor shedding. Soluble TNFR are constitutively released in the circulation[17], and their levels increase in the course of various disease states[18] and after TNF stimulation[19,20]. In cell culture systems, soluble receptors are rapidly produced in response to various stimuli such as TNF[21], lipopolysaccharide (LPS)[22], phorbol myristate

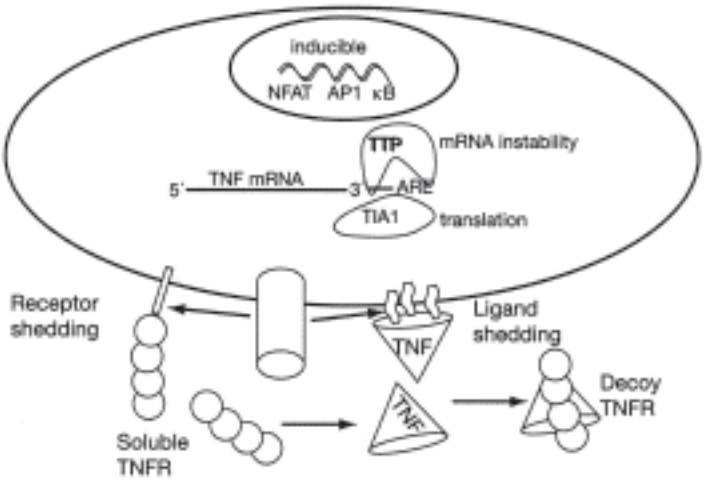

Figure 3. Regulation of TNF biosynthesis and bioavailability. The first point of regulation of TNF is at the transcriptional stage by adenosine and uridine (AU)-rich elements (ARE) in the 3' mRNA. The core sequence of ARE is a nucleotide pentamer containing the AUUUA motif. TNF-α mRNA contains a clustered AUUUA pentamer motif that confers instability, sensitivity to stimulus-driven stabilization, and stimulus-sensitive control of translational efficiency. The ARE interact with sequence-specific, RNA-binding proteins, which serve to coordinate instability or enhanced stability, depending on the circumstance. TNF-α ARE allowed the identification of T cell intracellular antigen-1-related protein (TIAR), T cell intracellular antigen-1 (TIA-1), and tristetraprolin (TTP) as TNF-α ARE-binding proteins. Whereas TIAR and TIA-1 bind the TNF-α ARE independently of the activation state of macrophages, the TTP-ARE complex is detectable upon stimulation with lipopolysaccharide (LPS). Moreover, treatment of LPS-induced macrophage extracts with phosphatase significantly abrogates TTP binding to the TNF-α ARE, indicating that TTP phosphorylation is required for ARE binding. The second point of regulation of TNF bioavailability is at the receptor level. TACE regulates TNF biosynthesis at the receptor level by cleaving membrane-bound TNF receptor (TNFR) to form soluble receptors capable of binding TNF. This process is referred to as receptor shedding. From Ware CF, TNF-related cytokines in immunity. In: Paul WE, editor. Fundamental immunology. 6th ed.; with permission from Wolters Kluwer/Lippincott Williams & Wilkins[6].

acetate, and interleukin 10, or after the activation of T cells[23] and neutrophils[24]. Shedding results in an acute decrease in the number of receptors on the cell surface and may transiently desensitize the cell to TNF action. The pool of soluble receptors competes with membrane-bound receptors for free TNF. At relatively low concentrations of soluble receptors, the TNF trimer is actually stabilized, preserving activity; however, as soluble TNFR concentration increases, the receptor binding sites on TNF become saturated, inhibiting binding to the cellular receptors, and thereby attenuating TNF activity[19].

Synthesis of TNF is determined by inducing stimuli, cell type involved, and activation status of cells; and amounts of soluble TNF are also regulated by the level of active TACE and the amounts of natural TACE inhibitors[25]. In organs involved in immune reactions, such as lymph nodes, gut, epithelium, and synovium, TNF is constantly transcribed at low levels, and contributes to homeostasis of lymphoid organs.

TNF and Lymphotoxin-α and Their Shared Receptors

TNF is closely related to LTα (formerly known as TNF-ß; Figure 4)[26]. LTα can exist as a homotrimer (LTα3) that is exclusively secreted owing to cleavage of its traditional signal peptide, a unique feature in the TNF superfamily. LTα also forms heterotrimers with LTß. LTα, like TNF, binds 2 receptors, TNFR1 (also known as TNFRp55/60), which is expressed on virtually all cell types, and TNFR2 (also known as TNFRp75/80), which is more restricted in tissue expression such as immune cells and endothelial cells. Both TNFR1 and TNFR2 are membrane glycoproteins that specifically bind TNF and LTα. However, LTα also binds HVEM (TNFRSF14), and the LTα heterotrimer binds the LTßR. TNFR1 and TNFR2 differ in their cellular expression profiles, affinities for ligands, cytoplasmic tail structures, and signaling mechanisms. Both receptors have structurally similar extracellular domains, but signal through distinct intracellular regions, with TNFR1 containing a death domain that is absent from TNFR2[16]. TNFR2 signaling is mediated through TNFR-associated factors. Studies examining the individual roles of TNFR1 and TNFR2 have identified distinct and separate outcomes, with TNFR1 signaling leading to inflammation and TNFR2 signaling leading to immunoregulation.

TNF-TNFR1 Interaction Mediates Inflammation and Cell Survival

Signaling through TNFR1 can initiate several cellular

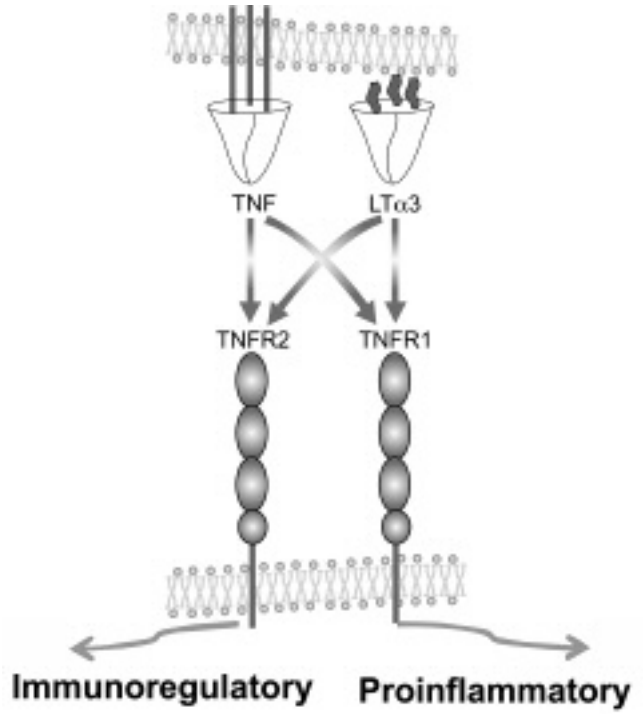

Figure 4. TNF-α and lymphotoxin α3 and their shared receptors. From Ware CF, TNF-related cytokines in immunity. In: Paul WE, editor. Fundamental immunology. 6th ed.; with permission from Wolters Kluwer/Lippincott Williams & Wilkins[6].

responses, including apoptosis, necrosis, cell survival, and inflammation. However, TNFR1 rarely triggers apoptosis unless the biosynthetic capacity of the cell is compromised, typically during infection by pathogens[27]. The interaction between TNF and TNFR1 is essential for the survival of cells such as the macrophage. Without this interaction, macrophages undergo disintegration and apoptosis. Cell survival is mediated through activation of the transcription factors nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) that induce macrophage survival genes and genes involved in the suppression of apoptosis[28]. Activation of NF-κB also induces genes such as IL-6, and chemokines, like IL-8 and RANTES, and enzymes involved in generating acute inflammatory mediators, e.g., 12-lipoxygenase. Therefore, cell survival and inflammation are closely connected and regulated.

TNF-TNFR2 Interaction Mediates Immunoregulation

The interaction between TNF and TNFR2 is crucial for several cellular processes, including proliferation, gene activation, and apoptosis. TNFR2 preferentially interacts with tmTNF over sTNF, suggesting that tmTNF is the primary activator of TNFR2[29]. This identifies tmTNF and TNFR2 involvement in the local response pattern in the microenvironment of tissues. Indeed, TNFR2 has been observed to initiate a switch in the cellular response pattern to TNF such that cells that are resistant to sTNF-induced apoptosis become susceptible to tmTNF and undergo activation-induced cell death (AICD)[29]. The process of AICD is of particular importance in the regulation and destruction of self-recognizing T cells. Without TNFR2 involvement, AICD is not initiated and is believed to play a role in autoimmune pathologies, including systemic lupus erythematosus (SLE)[30] and RA[31].

TNF Orchestrates Immune Response and Inflammation That Is Beneficial for Host Defense

Ligands and receptors in the TNF and LT systems have a variety of roles in the development and function of the immune system[4,32,33]. At low concentrations in tissues, TNF is thought to have beneficial effects, such as the augmentation of host defense mechanisms against infections. At high concentrations, TNF can lead to excess edema, erythema, inflammation, pain, and organ injury. Acute release of very large amounts of TNF during sepsis may result in septic shock.

However, much of the evidence for the role of TNF in immunity is based on studies with genetically deficient mice; therefore, the relevance to human immune system development and function is less clear. Although the mechanisms of resistance to bacterial and viral infections are complex and still under investigation, some data implicate TNF and LT as important components of host defense, particularly for intracellular bacteria such as Mycobacterium or Listeria. Killing of the intracellular bacteria within activated macrophages is primarily mediated by reactive oxygen species, including nitric oxide. Mice deficient in TNF, LTα, TNFR1, or LTßR are highly susceptible to experimental Mycobacterium, Listeria, and Staphylococcus infections compared with normal mice[34-36].

Mechanisms of host defense against intracellular pathogens, particularly *Mycobacterium tuberculosis*, in humans have not been as well studied as those in mice, but they have been extensively discussed in the context of the clinical safety of TNF antagonists.

The rationale for the first clinical study of a TNF antagonist in RA was based on the role of TNF in a proinflammatory cytokine cascade[37]. That many of the hallmarks of chronic inflammation, such as leukocyte recruitment, activation, and proliferation and production of inflammatory mediators, are reduced by TNF antagonist therapy confirms a mechanistic link to TNF. As more than 100 cytokines and chemokines have been identified, many of them studied in TNF antagonist-treated patients, the concept has emerged that TNF is at the top of a proinflammatory cytokine cascade[38].

THE ROLE OF TNF and DEVELOPMENT OF IMID

Dysregulation of immune mechanisms may lead to dysregulated TNF production at a site of immunological tissue injury, which in turn may sustain activation of innate

immune cells, leading to chronic inflammation. Depending on the location, organ-specific inflammatory pathology and tissue damage may ensue[39]. TNF, therefore, can play a significant role in the development of these pathologies and may provide an alternative mechanism for disease initiation or progression by altering cell differentiation, proliferation, or death.

As previously mentioned, TNF has a particularly important role in the regulation of a cascade of pathogenic events leading to RA, CD, Ps (Figure 5)[40], and other autoimmune diseases, illustrated by the rapid induction of production of cytokines and acute-phase proteins[38]. However, numerous studies have demonstrated that TNF acts within a complex network of cells and mediators of inflammation[41]. It is postulated that TNF acts as the key upstream trigger and mediator of downstream mechanisms and that a variety of positive and negative feedback loops control the chronicity and pathogenic outcomes of inflammation.

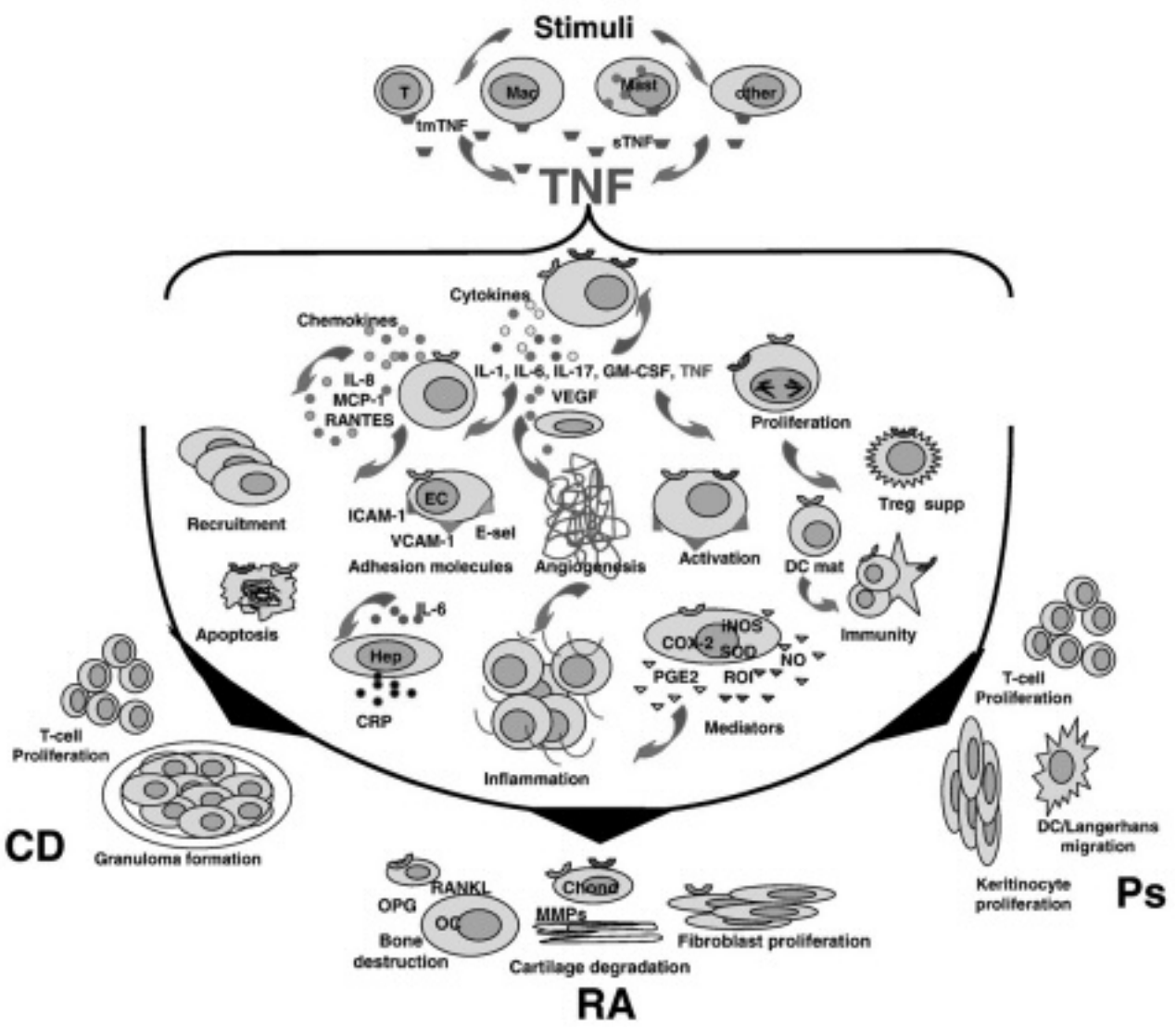

Figure 5. A cascade and network of cellular responses mediated by tumor necrosis factor (TNF) in immune-mediated inflammatory diseases (IMID). TNF is produced in high concentration by a number of cells in CD, RA, and Ps. Shown in the enclosed area are the cascade and network of cellular responses mediated by TNF and common to these 3 diseases. Mechanisms that are unique to each disease are shown outside the enclosed area. CD: Crohn's disease; Chond: chondrocyte; COX-2: cyclooxygenase-2; CRP: C-reactive protein; DC mat: mature dendritic cell; EC: endothelial cell; E-sel: E-selectin; GM-CSF: granulocyte-macrophage colony-stimulating factor; Hep: hepatocyte; ICAM-1: intercellular adhesion molecule 1; IL: interleukin; iNOS: inducible nitric oxide synthase; Mac: macrophage; Mast: mast cell; MCP-1: monocyte chemotactic protein-1; MMP: matrix metalloproteinases; NO: nitric oxide; OC: osteoclast; OPG: osteoprotegerin; PGE2: prostaglandin E2; Ps: psoriasis; RA: rheumatoid arthritis; RANKL: receptor activator for nuclear factor-κB ligand; RANTES: regulated upon activation, normal T cell expressed, and secreted; ROI: reactive oxygen intermediate; SOD: superoxide dismutase; (s/tm)TNF: (soluble/transmembrane); VCAM-1: vascular cell adhesion molecule-1; VEGF: vascular endothelial growth factor. From Tracey, *et al*, Pharmacol Ther 2008;117:244-79; with permission from Elsevier[40].

TNF-TNFR1 and IMID

It is widely accepted that TNF plays a critical role in RA by activating synovial fibroblasts and stimulating their proliferation[42]. Further, bone-marrow grafting studies in mice have demonstrated that the receptor TNFR1 is necessary for development of chronic inflammatory joint and intestinal diseases[43] (Table 2). Without TNFR1, mice do not develop arthritis, even when grafted into an ARE-deletion mutant that would otherwise result in an arthritic phenotype. Similar results are reported from crossbreeding studies using ARE-deletion mice and TNFR1-deletion mice[14]. As described, the TNF ARE-deletion mice in this study display the chronic pathologies of inflammatory arthritis and inflammatory bowel disease (IBD). When TNF ARE-deletion mice are bred into a TNFR1-deletion background, mice develop normally and do not display any sign of macroscopic illness. Further, the use of transgenic mice expressing Cre recombinase under the control of a collagen promoter cassette demonstrates the role of TNFR1 in the development of arthritis, CD-like IBD, and AS[43]. The findings identified TNFR1-expressing mesenchymal cells as the common target for TNF in the onset of IMID and also indicated a common mechanism explaining the synovial-gut axis often observed in human IMID. Taken together, these results point to a dominant role for TNFR1 in IMID.

TNF-TNFR2 and IMID

Recent studies have suggested a critical role for TNFR2 in the pathogenesis of CD. TNFR2 regulates immune homeostasis, therefore dysregulation of TNFR2 leads to disease states characterized by multiorgan inflammation and TNFR-associated factors (TRAF) activation. Studies carried out in transgenic mice that express constitutive yet physiologically relevant levels of TNFR2 demonstrate a link between TNFR2 upregulation and the development of a severe multiinflammatory syndrome[44]. TNFR2 expression is upregulated in colonic epithelial cells in murine colitis models as well as in patients with colitis and CD[45]. The upregulation of TNFR2, caused by key proinflammatory cytokines, may cause colonic inflammation-associated alteration in the intestinal epithelium. TNFR2 signaling associated with TRAF activation is involved in the pathogenesis of a murine model of CD[46], and TRAF activation has also been observed in human patients[47].

TNFR2 also contributes to the pathogenesis of SLE, RA, and AS. Circulating levels of soluble TNFR2 are elevated in these patients[48], and serum levels of soluble TNFR2 are believed to provide useful information about disease activity in patients with SLE[49]. Mortality due to cardiovascular disease in RA appears to be associated with elevated levels of soluble TNFR2. Thus, serum levels of soluble TNFR2 may be a useful biomarker in identifying RA patients at increased risk of premature death[50].

Table 2. Arthritis development following $Tnf^{\Delta ARE}$ bone marrow reconstitution of lethally irradiated recipients. From Armaka, *et al*, J Exp Med 2008;205:331–7; with permission[43].

Donor Genotype	Recipient Genotype	Arthritis Development
WT	WT	0/20
$Tnf^{\Delta ARE/+}$	WT	19/21
$Tnf^{\Delta ARE/\Delta ARE}$ $TnfRI^{-/-}$	WT	25/25
$Tnf^{\Delta ARE/+}$	$TnfRI^{-/-}$	0/8

ARE: adenosine- and uridine-rich elements; WT: wild-type.

TNF and TNFR in the Central Nervous System

TNF plays a central role in inflammation in the central nervous system (CNS) and has been implicated in the pathogenesis of several human inflammatory, infectious, and autoimmune CNS disorders. Studies using transgenic mice and gene knockout mice have demonstrated that TNF dysregulation triggers a neurological disorder characterized by ataxia, seizures, and paresis, with histopathological features of chronic CNS inflammation and white-matter degeneration[51]. When overexpressed by astrocytes, transmembrane TNF is sufficient to trigger CNS inflammation and degeneration, demonstrating that TNF-producing cells localize in the vicinity of astrocytes rather than neurons. Both soluble and transmembrane forms of TNF play critical roles in the pathogenesis of CNS inflammation and demyelination.

TNFR1 expression is necessary for TNF to trigger oligodendrocyte death and demyelination[52]. TNF released by glia cells in the CNS potently and selectively induces local oligodendrocyte apoptosis and inflammatory demyelination. These effects are abrogated in mice genetically deficient for TNFR1, demonstrating a dominant role for TNFR1-signaling pathways in TNF-mediated pathology. These results demonstrate that TNFR1 signaling in the CNS can have a potentially major role in demyelination observed in multiple sclerosis (MS).

It is important to note, however, that both infliximab and etanercept are contraindicated for patients with MS, based in part on the unexpected symptoms of demyelinating disease (paresthesia, optic neuritis, and confusion) developing in people with quiescent MS and new-onset cases of demyelinating disease, which reversed upon drug removal[53]. Further, that several inhibitors of TNF/LTα are linked to exacerbation of demyelinating disease in humans suggests that their common mechanism of action, blockade of TNF, is influencing pathogenesis. Failure of a TNF antagonist therapy in MS may be due to pleiotropic aspects of TNF actions. TNF may have important immunoregulatory functions, and be involved in tissue repair and regeneration, or host defense.

TNF INHIBITORS

TNF inhibitors show remarkable efficacy in a variety of

IMID. In spite of their significant efficacy, little is known about their mode of action *in vivo* and the factors that limit their scope of therapeutic application. All TNF inhibitors are antibodies with specificity for TNF, or in the case of etanercept, a chimera of the immunoglobulin molecule with ectodomain of TNFR2, and thus is specific for both TNF and LTα. All the currently approved TNF inhibitors share a common molecular mechanism of action, which is to competitively inhibit ligand-binding to their cognate receptors. However, the inhibitors differ in their physical and functional properties, including valency, effector functions, pharmacokinetics, and antigenicity (Figure 6 and Table 3). The clinical differences in efficacy of these TNF inhibitors in various IMID has led to discussions about how these human therapeutics might work *in vivo*.

Infliximab is derived from a mouse anti-human TNF, whereas adalimumab and golibumab are derived from human IgG antibody gene sequences; both are complete IgG1 molecules. Certolizumab is also an anti-TNF derived from a human antibody, but is a monovalent Fab fragment that has been chemically modified by addition of polyethyleneglycol to improve its pharmacokinetics, which are notoriously poor for Fab.

Primary Mechanism of Action

The primary mechanism of action of TNF inhibitors is to act as competitive antagonists to block soluble and membrane TNF from binding their receptors. TNF inhibitors neutralize TNF by recognizing antigenic epitopes on the ectodomain of TNF near or at the receptor-binding region, thus sterically hindering the TNF molecule in engaging its receptors[54]. Etanercept is a receptor-based therapeutic that binds directly to the receptor-binding region, which is formed by the interaction of 2 adjacent subunits in the TNF trimer. Without TNF binding to its receptor, the signaling cascade resulting in inflammation is silenced, thereby blocking the inflammatory responses.

Binding Characteristics

Currently available TNF inhibitors exhibit the ability to neutralize both sTNF and tmTNF (Table 3)[40]. All the TNF inhibitors bind membrane TNF with similar affinities, although there is some debate over whether the monoclonal antibodies infliximab and adalimumab bind with higher affinity to TNF than the receptor-based inhibitor etanercept[55]. The bivalent etanercept has a higher avidity for TNF compared to the monovalent, naturally shed TNFR.

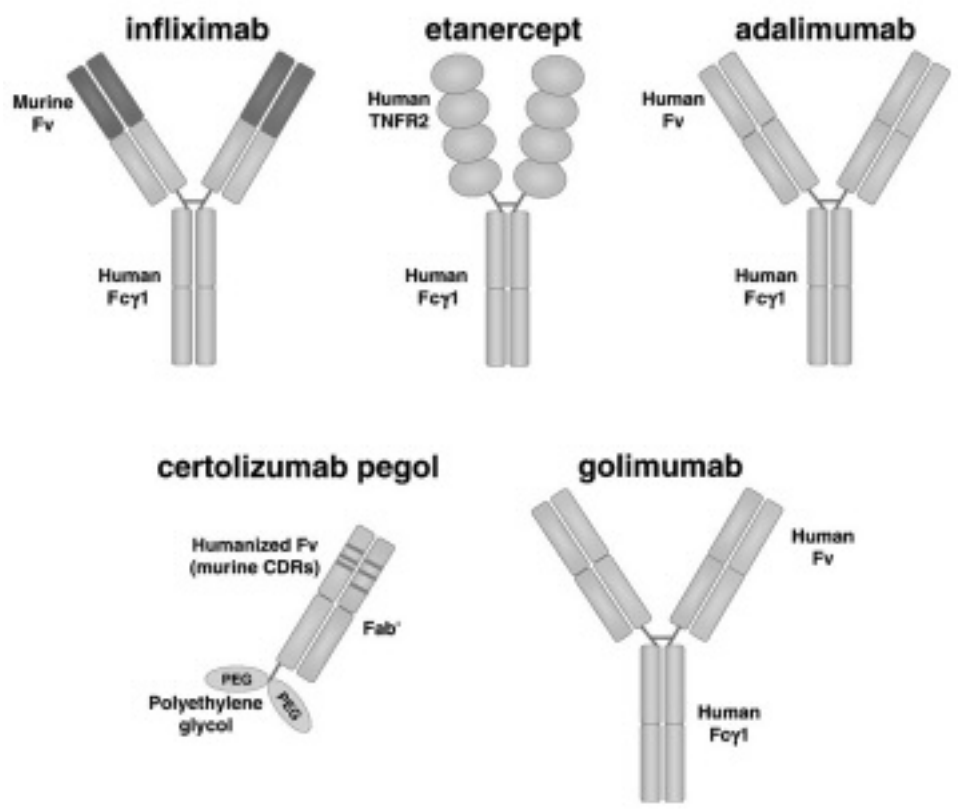

Figure 6. Simplified diagrams of the molecular structures of 5 TNF antagonists. Infliximab is a mouse/human chimeric monoclonal anti-TNF antibody of immunoglobulin (Ig) G1 isotype. Adalimumab and golimumab are fully human IgG1 monoclonal anti-TNF antibodies. Etanercept is a fusion protein of TNFR2 (p75) and the Fc region of human IgG1. Certolizumab is a PEGylated Fab' fragment of a humanized IgG1 monoclonal anti-TNF antibody. From Tracey, *et al*, Pharmacol Ther 2008;117:244-79; with permission from Elsevier[40].

Table 3. Biochemical and mechanistic profile of TNF antagonists. Adapted from Tracey, *et al*, Pharmacol Ther 2008;117:244–79, with permission from Elsevier[40].

	Infliximab	Etanercept	Adalimumab	Certolizumab	Golimumab
Class	mAb	Fc fusion protein	mAb	mAb fragment	mAb
Structure	Mo/Hu chimeric IgG1κ	Hu sTNFR2-Fcγl	Hu IgG1κ	PEG-Hu IgG1κ Fab	Hu IgG1κ
Molecular weight, kDa	150	120 ?	150	~95	150
Specificity	TNF	TNF/LTα	TNF	TNF	TNF
TNF ligands	sTNF, tmTNF	sTNF, tmTNF	sTNF, tmTNF	sTNF, tmTNF	sTNF, tmTNF
LT ligands	None	LTα3, LTα2ß1	None	None	None
Neutralization potency					
sTNF (low conc)	Moderate	Strong	Moderate	ND	ND
sTNF (high conc)	Strong	Strong	Strong	Strong	ND
tmTNF binding	Strong	Moderate	Strong	Strong	ND

ND: no data available; mAb: monoclonal antibody; Hu: human; Mo: mouse; LT: lymphotoxin; PEG: polyethyleneglycol; TNF: tumor necrosis factor; TNFR: TNF receptor; tmTNF: transmembrane TNF; sTNF: soluble TNF; conc: concentration.

Infliximab is able to bind both the monomeric form as well as the biologically active trimeric form of TNF. Etanercept binds only the native trimeric form of TNF and LTα[55]. Adalimumab, infliximab, etanercept, and certolizumab have similar affinities for soluble TNF, but with differing on- and off-rates. Etanercept has a faster binding on-rate and a faster dissociation off-rate to soluble TNF than does infliximab or adalimumab. The difference in the specificity of etanercept, which binds both TNF and LTα, from the monoclonal antibodies, which bind only TNF, might also explain some differences in treatment outcomes using these agents[4,56].

Pharmacokinetic Profile

The pharmacokinetic profiles of TNF inhibitors differ (Table 4) and may contribute to the different efficacies of these antagonists. Etanercept is rapidly cleared from serum at 72 ml/h (compared to 11 ml/h for infliximab and 12 ml/h for adalimumab), and has the shortest half-life at 4–5 days. Intact IgG1 has a long half-life, which is reflected in the longer half lives of infliximab (8–10 days) and adalimumab, golimumab, and certolizumab (10–20 days). Etanercept has the lowest maximum steady-state concentration of 1.1 μg/ml (compared to 118 μg/ml for infliximab and 4.7 μg/ml for adalimumab). Taken together, these differences suggest that the anti-TNF IgG may provide longer coverage than etanercept.

Secondary Mechanisms of Action

Secondary mechanisms of action have been suggested to account for some of the differences in efficacy of antibody versus receptor-based inhibitors. For instance, TNF antibodies have been shown to mediate complement-dependent[57,58] and antibody-dependent cell-mediated cytotoxicity (ADCC) when incubated with cells expressing tmTNF, thus acting to eliminate inflammatory cells[59,60]. Binding or cross-linking of tmTNF by bivalent IgG has been suggested to induce a reverse (outside to inside) intracellular signaling cascade[41,54], although such pathways by TNF-related ligands are undefined. These alternative mechanisms all depend on bivalent IgG and an intact Fc domain. Although not a true controlled experiment, a strong argument against these secondary mechanisms of action is that certolizumab, which is unable to crosslink tmTNF or activate ADCC or complement, displays very similar efficacy in IMID as bivalent IgG[59].

Another unexplained feature of blocking TNF is that in some patients the effects last longer than the drug is present

Table 4. Pharmacokinetics of TNF inhibitors. Adapted from Tracey, *et al,* Pharmacol Ther 2008;117:244–79, with permission from Elsevier[40].

	Infliximab	Etanercept	Adalimumab	Certolizumab	Golimumab
Half-life, days	8–10	4	10–20	~14	7–20
Volume of distribution, V_{ss}	4.3 ± 2.5 l[a]	8.0 l[b]	4.7–6.0 l[c]	ND	6.9 l[d]
Clearance, C_L	11 ml/h[a]	72 ± 5 ml/h[e]	12 ml/h[c]	ND	16.7 ml/h[f]
C_{max}	118 μg/ml[a]	1.1 ± 0.6 μg/ml[e]	4.7 ± 1.6 μg/ml[g]	ND	70.8 ± 18.9 μg/ml[h]

[a] 5 mg/kg intravenous (IV); [b] V_{ss} (volume of distribution at steady state) estimated as sum of Vc + Vp for volumes of distribution in the central and peripheral compartments, respectively, from a 2-compartment population pharmacokinetic model based on 10 studies with 2–25 mg IV or subcutaneous (SC) single dose or biw; [c] 0.25–10 mg/kg IV; [d] V_{ss} estimated as sum of Vc + Vp for volumes of distribution in the central and peripheral compartments, respectively, from a 2-compartment population pharmacokinetic model based on data from 0.1–10 mg/kg IV; [e] based on data from 2–20 mg IV and 2–50 mg SC; [f] 0.1–10 mg IV; [g] 40 mg SC; [h] 3 mg/kg IV. ND: no data available.

in the circulation, although the beneficial effects are not permanent. The loss of TNF signaling may lead to fundamental changes in the immune system, such as changes in lymphoid tissue architecture or changes in T regulatory cells, which may induce or help reestablish tolerance and homeostasis.

EFFICACY OF TNF INHIBITORS

The efficacy of TNF inhibitors varies: some inhibitors show clear benefit in certain IMID, while others have little or no effect (Table 5). However, about one-third of patients with IMID do not respond to any anti-TNF treatment and in some diseases TNF inhibitors are contraindicated. The reasons for these differences remain unknown, but contributions from genetic makeup of the patients to underlying mechanisms of pathogenesis are undoubtedly important.

All currently available anti-TNF inhibitors are effective in treating RA. Of particular importance is their ability to improve symptoms and physical function, and to slow radiographic progression[61-63]. Etanercept, infliximab, and adalimumab are efficacious in treating moderate to severe Ps, showing improvement in severity [Psoriasis Area and Severity Index (PASI) score], remission and relapse rates, and health-related quality of life[64,65]. Adalimumab has also proven to be effective in patients with moderate to severe Ps who fail to respond to etanercept[66]. Etanercept, infliximab, and golimumab show efficacy for the treatment of active and progressive PsA, exhibiting beneficial effects on both joint and Ps symptoms and on functional status[67,68]. Adalimumab is efficacious in patients with severe plaque Ps and PsA and mediates a decisive regression of joint/skin involvement[69]. Adalimumab, etanercept, and infliximab are clinically effective in AS in relation to ASAS (Assessment in Ankylosing Spondylitis), BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), and BASFI (Bath Ankylosing Spondylitis Functional Index)[70]. Indirect comparisons of treatments for AS are limited and do not show a significant difference in efficacy between the presently available agents. Infliximab is effective in closing fistulas and significantly reducing hospitalizations, surgeries, and procedures in patients with fistulizing CD[90]. Certolizumab has been shown to be effective in patients with moderate to severe CD[91]. Although infliximab is highly effective in treating CD, some patients develop an attenuated response over time. Adalimumab offers good efficacy in infliximab-resistant or intolerant patients and is well tolerated without signs of immunogenicity[92]. Adalimumab is also well tolerated in pediatric CD patients, mediating a complete or partial response without serious adverse events[93]. In contrast, etanercept shows no efficacy in the treatment of CD[79]. As mentioned, etanercept is also not efficacious in treating sarcoidosis, Wegener's granulomatosis, or uveitis. It has been postulated that the different disease mechanisms might account for varying efficacy, that the role of TNF might change from one stage of disease to another, or that the varying genetic makeup of patients contributes to differences.

Patient Genetic Makeup

The genetic makeup of patients may influence their response to biological treatments. For example, RA patients with a TNF-308 G/G genotype respond better to infliximab treatment than patients with A/A or A/G genotypes[94]. This observation holds true for patients with PsA or AS[95]. Therefore, TNF-308 genotyping may be a useful tool for predicting response to infliximab treatment. RA patients with a TNF-308 G/G genotype also respond better to etanercept and adalimumab than patients with a TNF-308 A/G genotype[96,97]. Genome-wide association studies of IMID in progress will be important new sources of information for helping to predict patient responses to TNF inhibitors[98,99].

CONCLUSION

TNF-related ligands and their receptors act as key communication systems between cells of the immune system that mediate inflammation and tissue destruction. These cytokines have evolved as part of a complex system of innate immunity and host defense, particularly against microbial infections, and can either enhance or suppress adaptive immunity.

Table 5. Efficacy of tumor necrosis factor antagonists in different IMID.

Efficacy in	Infliximab	Etanercept	Adalimumab	Certolizumab	Golimumab
RA[71-76]	Yes	Yes	Yes	Yes	Yes
PsA[71-73,75-77]	Yes	Yes	Yes	ND	ND
AS[71-73,75,76,78]	Yes	Yes	Yes	ND	ND
CD[74,79,80]	Yes	No	Yes	Yes	ND
UC[81]	Yes	ND	ND	ND	ND
Psoriasis[82-84]	Yes	Yes	Yes	ND	ND
JIA[85,86]	Yes	Yes	ND	ND	ND
WG[87,88]	Yes	No	ND	ND	ND
Sarcoidosis[89]	Yes	No	ND	ND	ND

PsA: psoriatic arthritis; AS: ankylosing spondylitis; UC: ulcerative colitis; JIA: juvenile idiopathic arthritis; WG: Wegener's granulomatosis; ND: no data. Adapted from Tracey D, Pharmacol Ther 2008;117:244-79; with permission from Elsevier[40].

Studies in humans with TNF inhibitors have demonstrated that TNF plays a pivotal role in the pathogenesis of several IMID including RA, PsA, Ps, AS, and IBD. The biosynthesis and bioavailability of TNF are tightly regulated at both transcription and receptor-binding levels. TNF-binding to TNFRI is typically associated with inflammation and cell survival, whereas binding to TNFR2 is usually associated with immunoregulation and apoptosis.

Although all currently available TNF inhibitors show remarkable efficacy in joint-related IMID, their efficacy in other IMID-related conditions (i.e., IBD, uveitis) varies. This may be due to differences in their molecular actions and pharmacokinetic properties. Better understanding of mechanisms of action of TNF antagonists, and related distinctions between the agents, will continue to emerge with the discoveries of other TNF-based therapies and with broader use of these agents in clinical practice.

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