Journal of Medical Sciences

ISSN 1682-4474

science alert

ANSInet
an open access publisher
http://ansinet.com

Review Article

J. Med. Sci., 13 (4): 226-235
15th May, 2013
DOI: 10.3923/jms.2013.226.235

Tumor Necrosis Factor as Mediator of Inflammatory Diseases and its Therapeutic Targeting: A Review

[1]Kuldeep Dhama, [2]Shyma K. Latheef, [3]Hari Abdul Samad, [4]Sandip Chakraborty, [5]Ruchi Tiwari, [5]Amit Kumar and [6]Anu Rahal

Signaling molecules of immune system are cytokines that may either stimulate or suppress the responses of various cells involved in host immune mechanisms and Tumor Necrosis Factor (TNF) is one of the leading members of the group of cytokines. TNF-α from activated macrophages and LT-α/TNF-B from T cells have now become representatives of a distinctive superfamily of cytokine ligands (TNF ligand superfamily) along with their corresponding receptors (TNF receptor superfamily); altogether constituting the TNF Superfamily. These are highly conserved proteins, found in all mammals having important ligand members which interact with the either of the two receptors, TNFR1 and TNFR2, that initiate varied signaling cascades leading to diverse cellular responses. It has been established that the appropriate regulation of TNF ligand and receptor interactions and functions are crucial for the proper immune system activity. Excessive production of various TNF cytokines has been attributed with the development of an array of autoimmune as well as inflammatory conditions. TNF cytokines help to reduce mortality due to cardiovascular diseases. Therapeutic TNF blockers include:monoclonal antibodies to TNF (Infliximab and Adalumimab) and TNF receptor fusion proteins (Etanercept and Lenercept) and are effective against rheumatoid arthritis; ankylosing spondylitis; psoriasis and asthma. Preclinical studies conducted in murine models and the pivotal role played by the TNF superfamily in cytokine mediator system will make it easier for researchers as well as scientists to develop novel drugs in near future. This review has covered all these aspects concerning TNF as mediator of inflammatory diseases and its therapeutic targeting.

Key words: Tumor necrosis factor, cytokine, inflammation, autoimmunity, ligand, malignancy, disease, therapy

[1]Division of Pathology, Indian Veterinary Research Institute, Izatnagar, Bareilly (U.P.)-243122, India
[2]Immunology Section, Division of Veterinary Biotechnology, India
[3]Division of Animal Physiology and Climatology, Indian Veterinary Research Institute, Izatnagar, Bareilly (U.P.)- 243122, India
[4]Animal Resources Development Department, Pt. Nehru Complex, Agartala, Pin-799006, India
[5]Department of Veterinary Microbiology and Immunology, India
[6]Department of Veterinary Pharmacology and Toxicology, Uttar Pradesh Pandit Deen Dayal Upadhayay Pashu Chikitsa Vigyan Vishwa Vidyalaya Evum Go-Anusandhan Sansthan (DUVASU), Mathura (U.P.)- 281001, India

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

For further information about this article or if you need reprints, please contact:

Kuldeep Dhama
Division of Pathology,
Indian Veterinary Research Institute, Izatnagar,
Bareilly (U.P.)-243122, India

ANSInet
Asian Network for Scientific Information

INTRODUCTION

Signaling molecules of immune system are cytokine that may either stimulate or suppress the responses of various cells involved in host immune mechanisms and interact or convey the essential messages for the proper functioning of defense systems against numerous pathogens or disease conditions (Chauhan and Dhama, 2008; Dhama *et al*., 2011). They trigger signal-transduction pathways by binding to receptors on a target cell (that ultimately alter gene expression in these cells). They are involved in both innate and adaptive immunity play important role as adjunctive immunomodulators in a variety of infectious diseases (Darnell Jr., 1997; Bach *et al*., 1997; Chang *et al*., 2004; Tizard, 2004). Tumor Necrosis Factor (TNF) is one among the most studied and central pro-inflammatory cytokines (Gillett *et al*., 2010). It was first identified in 1984, in which the two forms, TNF-β and LT-α (otherwise called lymphotoxin or TNF-α), were isolated; TNF-β from activated macrophages and LT-α from T cells. These proteins have now become representatives of a distinctive superfamily of cytokine ligands (TNF ligand superfamily) along with their corresponding receptors (TNF receptor superfamily); altogether constituting the TNF Superfamily (Croft *et al*., 2012). Most of the members are expressed by immune cells or can target immune cells and thereby exert a wide range of actions including the production of inflammatory chemokines and cytokines, promoting cellular growth, differentiation and survival etc. TNF-β induces the expression of selectin which bind to mucins expressed by circulating neutrophils and this binding mediates the attachment or wandering neutrophils to the vascular endothelium (Gabay and Kushner, 1999; Dhama and Chauhan, 2008). Cytokine like TNF-β also induces coagulation; increases the vascular permeability and induces increased expression of adhesion molecules on vascular endothelial cells along with playing a central role in chronic inflammation as well as autoimmunity and malignant diseases like cancer. For maintaining the homeostasis of the immune system; inflammation as well as host defence, TNF plays a major role but there exists a dark side to this powerful cytokine (especially clear in middle aged and old aged people) (Balkwill, 2006; Dhama *et al.,* 2008).

Tumor Necrosis Factor (TNF) which was described as a key cytokine for inflicting necrosis of tumors has now been recognized as a key regulator of the inflammatory responses. Many scientific researches have concluded that TNFSF ligand-receptor interactions and signaling pathways are active in mediating several of the inflammatory and autoimmune diseases (Watkins *et al*., 1995). TNF ligands were identified to have central role in a variety of inflammatory conditions viz., rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, psoriasis, graves' disease, SLE, multiple sclerosis, diabetes, asthma etc. (Croft *et al*., 2012). Moreover various genetic polymorphisms in the proteins of this superfamily have been associated with the susceptibility to developing disease (Haritunians *et al*., 2010; Jung *et al*., 2010).

As the involvement of the TNF superfamily ligand and receptor molecules in the incidence of the above pathological conditions has been established, it is clear that the inhibition of these communications can prevent the downstream signaling pathways, leading to the suppression of inflammatory immune cells and thereby diminishing the pathology of autoimmune and inflammatory diseases (Locksley *et al*., 2001). Several TNF blocking drugs have been presented with therapeutic success and based on the success of these therapies, attention is put for further developments (Thompson *et al*., 2011; Dhama *et al*., 2013).

TNF SUPER FAMILY

The Tumor Necrosis Factor (TNF) superfamily consists of approximately 50 membrane-bound and soluble proteins. About 350-450 million years ago there was evolution of ligand and receptor molecules along with adaptive immune system (Croft, 2009). These are highly conserved proteins, found in all mammals (Croft, 2003a). Important ligand members of this family include TNFα, LT-α, LT-β, OX40L, TRAIL, CD40L, CD27L, CD30L, FASL, 4-1BBL, OPGL, LIGHT, APRIL, DR3, DR4, DR5, RANK and TALL-1 etc. (Ashkenazi and Dixit, 1998; Shu *et al*., 1999; Croft, 2003b; Kodama *et al*., 2005). With the exception of LT-α all ligand members are type-II membrane proteins forming the hallmark of ligand family with C-terminal extracellular domain having conserved region of 150-amino acids that folds into homotrimers formed by β-pleated sheet. It can generate a soluble functional form when released by proteiolytic degradation. But unlike other protein families of notable homology, these proteins display only about 20±25% homology at the protein level (Gillett *et al*., 2010; Croft *et al*., 2012).

Type I transmembrane proteins constituting a variety of cysteine-rich motifs in their extracellular domains (disulphide bridge-based structural modules) are the members of receptor superfamily. There are two distinct types of TNF receptors; type I and type II with molecular sizes 55 kD and 75, respectively. A pre-ligand assembly domain (PLAD) has been described recently for a subset of receptors, including Fas, TNF-receptor I (TNF-RI) and CD40 which is thought to facilitate homotypic association

between monomeric receptor subunits, by which the receptor complexes are capable of responding rapidly to environmental cues. With the emergence of adaptive immunity, an extended family gives rise to this core family of ligand-receptors through en-bloc gene duplication events (partially from single ancestral genes). They include the TNF superfamily homologue Eiger and the TNF-RSF homologue Wengen (Clark *et al*., 2005). Regarding the expression, different molecules of TNF ligand-receptor family are not ubiquitously expressed. The expression of several of these molecules is increased following immune-cell activation and this suggests that they have a central role in modulating immune responses. Studies of TNFRs expressed by conventional T cells and their ligands expressed by antigen-presenting cells (ApCs) has led to the hypothesis that antigen recognition by T cells engages and bidirectionally activates TNF-TNFR pair that contribute to the immune cells (including T lymphocytes) effector responses (Croft, 2003a, 2009; Fang *et al*., 2008).

Cytokine binding to some TNF receptor family members, such as TNF-RI, TNF-RII and CD40 favour the recruitment of TNF receptor-associated factors (TRAFs) to the cytoplasmic domains of the receptors. The TRAFs activate transcription factors like nuclear factor KB (NF-KB) and activation protein-I (API). Cytokine binding to other family members, such as TNF-RI, leads to recruitment of an adapter protein that activates caspases and triggers apoptosis. Thus, different members of the TNF receptor family can induce gene expression and cell death and some can do both. TNFRI knockout mice show more impaired host defense than do TNF-RII knockout mice, suggesting that TNF-RI is more important for the function of the cytokine. Then within 10-20 min, on ligation with TNF-β, TNFR I get trimerized and recruits various adapter molecules. This will activate NF-κB, inducing several anti-apoptotic genes (Complex I formation) and survival signal (Lee *et al*., 2002). This is followed by (more than 2-3 h) by an endocytosis of receptor complex resulting in the dissociation of certain adapter proteins (TRAF-2, RIP) and recruitment of Fas-associated Death Domain (FADD) and procasepase-8 to form Death-inducing Signaling Complex (DISC). In the DISC, caspase-8 is activated and released into the cytoplasm where it activates effector caspases to induce apoptosis (Croft, 2003a).

ACTION AS MEDIATORS OF INFLAMMATORY PROCESS

TNF ligands interacts with the either of the two receptors, TNFR1 and TNFR2, that are differentially expressed on cells and initiate varied signalling cascades, leading to diverse cellular responses viz., cell death, proliferation, differentiation and migration (Bradley, 2008). Various pro-inflammatory changes are the outcomes of TNF responses of vascular endothelial cells that lead to adhesion and trans-endothelial migration of leukocytes along with vascular leak. TNF also induces the expression of certain pro-coagulant proteins and down-regulate anticoagulant protein, thereby inducing intravascular thrombosis (Mark *et al*., 2001; Croft, 2003a). Another major role of TNF is as a modulator of host defense mechanism against infectious agents; especially gram negative bacterial organisms. This role has been confirmed by studies conducted in mice deficient in TNF receptor. Those mice had severely reduced clearance of the bacterium *Listeria monocytogenes* and immediately yielded to this infection (Pfeffer *et al*., 1993; Rothe *et al*., 1993; Bradley, 2008). There are also evidences that increased serum TNF levels were found in the cases of uncomplicated Plasmodium falciparum malaria and markedly increased in cases of fatal cerebral malaria (Bradley, 2008). This indicates that TNF is physiologically an important factor for the normal defense against infections, but can be harmful if the production is inappropriate or extreme. In hepatic diseases there will be reduced TNF production and accompanying incapacity to fight infection (Gillett *et al*., 2010).

In order to develop and modulate immune system, majority of members of ligand family play important roles as lymphoid-enriched tissues are their main expression sites (Khare *et al*., 2000). TNF, which is predominantly from the macrophages, is a key mediator of inflammatory responses and defenses (Tracey and Cerami, 1994; Khare *et al*., 2000). Fas ligand mainly synthesized by activated T cells, modulates thymocyte apoptosis mediated by T cell receptor (Castro *et al*., 1996). CD40L, which is also expressed by activated T cells, signals for B cell survival and proliferation as well as immunoglobulin isotype switching (Khare *et al*., 2000; Gillett *et al*., 2010).

Many members of the TNFSF were recognized to modulate some non-lymphoid cells also. TNF which was initially described as a circulating factor, causing necrosis of tumour, has since been identified as a key regulator of the inflammatory responses. TNF ligands were identified to have central role in a variety of inflammatory conditions viz., rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, psoriasis, graves' disease, SLE, multiple sclerosis, diabetes, asthma etc (Croft *et al*., 2012).

In approximately 1% of population Rheumatoid Arthritis (RA) develops most commonly. The condition is characterized by persistent synovitis resulting in progressive damage, erosion of adjacent bone and cartilage and systemic inflammation, leading to chronic

disability. Synovial hyperplasia accompanied by angiogenesis is a prominent feature of the condition (Geiler *et al*., 2011). Predisposing causes to the condition include genetic causes, autoantibodies and environmental factors etc. Several pro-inflammatory cytokines viz., TNF, IL-1, GM-CSF, IL-6, are produced within the inflamed joint cavity. Because of their predicament in the inflammatory reaction cascade, tumor necrosis factor ligands proven to be the most important cytokines involved in rheumatoid arthritis (Geiler *et al*., 2011).

Crohn's disease-like inflammatory bowel disease and ulcerative colitis are inflammatory conditions inflicting the lamina propria of intestine and an over-expression and increased immunoreactivity of various TNF family members have been demonstrated to be involved with the development of these inflammatory conditions (Sands *et al*., 2004). Patients affected with Crohn's disease are more prone to another autoimmune condition called Ankylosing spondylitis, which is an inflammatory arthritis, particularly affecting the spine along with sacroiliac joints. In those patients with this condition, elevated serum levels of various TNF proteins were identified that correlates the role of TNF in the disease incidence (Lange *et al*., 2000; Francois *et al*., 2006).

Systemic Lupus Erythematosus (SLE) is an autoimmune disease in which there will be production of autoantibodies that are specific for the DNA, RNA or various proteins associated with nucleic acids. This will lead to the formation of immune complexes in small blood vessels, especially in the kidneys (Yang *et al*., 2009). The affected patients with SLE usually found to have abnormal B- and T-cell function (Croft, 2009; Croft *et al*., 2012). Psoriasis, an autoimmune and inflammatory disorder affecting the skin, is characterized by the presence of psoriatic plaques, formed by inflammatory cell infiltration and hyperkeratotic lesions. A study conducted in patients with psoriasis has shown an upregulated expression of TNF receptors in blood vessels associated with dermal layers (Chaudhari *et al*., 2001; Gottlieb *et al*., 2004; Bradley, 2008).

TNF exerts its action in the central nervous system also, where its main sources are microglia and astrocytes, in response to infections, inflammations, ischaemic as well as traumatic injuries. But it has been shown to have both detrimental and favorable effects in brain, depending upon the conditions (Arnett *et al*., 2001; Bradley, 2008). In murine model, blockage of TNF during ischaemic injury to the brain resulted in amelioration of the condition (Nawashiro *et al*., 1997) but in case of experimental autoimmune encephalomyelitis, those with lack of TNF were highly susceptible to the condition and treatment using TNF supplementation reduced the condition. SLE is a multiple organ system related autoimmune disease with exceptionally diverse clinical manifestations. Various studies have shown that TNF ligand-receptor pair has been implicated in this autoimmune condition also (Croft, 2009).

TNF has its role in cardiovascular diseases also, in which the disease pathology has been found to be associated with the exacerbated level of various TNF cytokines. Variety of pathological conditions of cardiovascular system viz. atherosclerosis and myocardial infarction; myocarditis, heart failure and cardiac allograft rejection and vascular endothelial cell responses have been implicated with TNF. Several studies point out that certain chronic inflammatory and autoimmune conditions such as rheumatoid arthritis have predisposition towards cardiovascular diseases. This predisposition of increased cardiovascular risk has been found to be in association with elevated serum level of inflammatory mediators, mainly TNF and there also evidences for amelioration of these conditions on anti-TNF therapy (Wolfe and Michaud, 2004; Croft, 2009).

The key role of TNF is connected with the incidence of several inflammatory conditions in respiratory system also and some of those conditions include asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, chronic bronchitis etc (Mukhopadhyay *et al*., 2006). In the case of asthma, leukocytes collected from bronchiolar lavage of the patients were to have augmented release of TNF and it was shown to play role in bronchial hyper-responsiveness by inflicting inflammation and remodeling. TNF is associated with the pathogenesis of various renal diseases like glomerulonephritis, renal transplant rejection, renal ischaemia etc. (Al-Lamki *et al*., 2005). It has been found that in case of diseases associated with renal inflammation, difference in the signalling of TNF receptor subtypes leads to difference in the efficacy and adverse effects of various blocking agents (Al-Lamki *et al*., 2010).

DIFFERENT TNF LIGAND RECEPTOR INTERACTIONS IN MEDIATING INFLAMMATORY AND AUTOIMMUNE DISEASES

OX40-OX40L: One among the TNF receptor-ligand pair is OX40-OX40L which is proinflammatory in function. Various knockout studies have proven that they play major role in the development of autoimmune disease like Rheumatoid Arthritis (RA), inflammatory colitis, diabetes, Multiple Sclerosis (MS), asthma and atherosclerosis in murine models (Croft, 2009; 2010). Compared to healthy individuals, in case of individuals with mild asthma there is upregulation of expressed OX40 and OX40L in the submucosa of bronchi (Siddiqui *et al*., 2010). Mice

deficient in OX40L suffer from polymicrobial sepsis showing improved survivality and reduction in production of cytokine and damage of organ. Ocular inflammation is also found to have diminished in murine autoimmune uveitis thereby widening the scope of disease control by OX40 and OX40L interaction (Zhang *et al*., 2010). In a model of coxsackie virus B3 driven myocarditis, heart inflammation shown to be ameliorated by the blockade of OX40L, thereby leading to increased survivability (Fousteri *et al*., 2011). This indicates the connection of this ligand-recceptor interaction with atherosclerosis development (Croft, 2009; 2010). This interaction has also been proven in correlation with the risk of development of Systemic Lupus Erythematosus (SLE). OX40 has been found to be associated with lupus nephritis condition by demonstrating its increased expression on Th17 cells which infiltrate kidney parenchyma (Dolff *et al*., 2010).

CD30: CD30, known for its increased expression on malignant tumors like Hodgkin's lymphoma, has been proven for its role in autoimmune diabetes and asthma. Blockage of CD30-CD30L interaction was found to reduce the development of these diseasevin the NOD mouse models (Oflazoglu *et al*., 2009). In case of colitis, the blocking of CD30L interactions lead to the suppression of trinitrobenzene sulfonic acid (TNBS)-induced colitis (Sun *et al*., 2008; 2010). CD40-CD40L interaction, which was described to modulate B cell activity and isotype switching has now been identified to promote various inflammatory and autoimmune conditions in murine models. These conditions include Graves' disease, SLE, RA, MS, diabetes, asthma, psoriasis, inflammatory bowel disease etc. (Peters *et al*., 2009). CD40L is also expressed by platelets which indicate that it may be involved in the development of atherosclerosis (Lievens *et al*., 2010). This is supported by the finding that platelets from CD40L-deficient mice were fail to adhere on vascular endothelium *in vivo* and unable to form aggregates of platelet and leukocyte atherosclerotic lesions (Lievens *et al*., 2010; Croft *et al*., 2012).

4-1BB: 4-1BB, another important member of this superfamily, was identified as a stimulatory molecule of activated T cells, has now been shown to express on activated antigen presenting cells and other cell types. Various cancer studies conducted in murine tumor models have shown that they contributes for the augmented activity of T cytotoxic cells and NK cells (Tansey and Szymkowski, 2009). 4-1BB may also control sepsis and biliary cirrhosis. This ligand has shown to exert its effect on sepsis in which the ligand deficient mice exhibited reduced mortality in a sepsis model. In case of primary biliary cirrhosis, the expression of 4-1BBL has shown a positive correlation with the disease markers of serum viz., interleukin (IL)-18, bilirubin, glutamyltransferase etc. (Nguyen *et al*., 2009; Croft *et al*., 2012).

CD70-CD27 l: CD70-CD27 ligand-receptor interaction has been found to be between a range of immune cells and also between immune and some nonimmune cell types. This interaction is implicated in several autoimmune diseases especially in the case of Experimental Autoimmune Encephalomyelitis (EAE), ie mouse models of multiple sclerosis and also in SLE of humans and murine models (Nolte *et al*., 2009; Croft *et al*., 2012). Recent studies with collagen-induced murine models of rheumatoid arthritis shown to had diminished disease symptoms upon anti-CD70 antibody therapy. Expression of CD70 is reported to be Th1 cell-specific which correlates with the finding that therapies involving CD70 blockade had its ameliorating effects on Th1-driven hypersensitivity reactions and contact hypersensitivity reactions, however no effect on the extent of pathology of Th2-type disease models as in the case of Th2-driven asthma and experimental allergic conjunctivitis (Sumi *et al*., 2008; Behrendt and Hansen, 2010).

DR3-TL1A: Death receptor 3 (DR3) and TNF-like factor 1A (TL1A) interactions are associated with Th1 co-stimulation and these molecules are now been implicated in the pathology of gut inflammatory conditions (Croft, 2009) such as IBD, ulcerative colitis and Crohn's disease (Tremelling *et al*., 2008; Haritunians *et al*., 2010). There is also evidence of increased TL1A expression in connection with the development of T cell-dependent inflammatory small bowel pathology. In addition to Th1 cells the expression of DR3 is found on Th17 cells (Meylan *et al*., 2011; Croft *et al*., 2012). The TL1A-DR3 interaction is not restricted only to those diseases which are regulated by Th1- or Th17 cells, but also by Th2 cells. In anti-TL1A therapy to Th2-driven murine models of asthma, it displayed impaired expression of Th2 cytokines, leading to the suppression of airway inflammation and mucus production (Zhang *et al*., 2009). Glucocorticoid-induced TNF receptor-related protein (GITR) and its ligand (GITRL): The GITR-GITRL interaction pathway has reported to be active in the development of type 1 diabetes and pancreatitis. This has been proven by the study in NOD mice using agonist anti-GITR antibody therapy, leading to a higher incidence of diabetes (Galuppo *et al*., 2011; Croft *et al*., 2012).

THERAPEUTIC TARGETING OF TNF

It has been established that the appropriate regulation of TNF ligand and receptor interactions and functions are crucial for the proper immune system activity. Excessive production of various TNF cytokines has been attributed with the development of an array of autoimmune as well as inflammatory conditions, some of which are discussed above. In order to suppress the immunopathology and disease progression of these conditions, therapies should be aimed mainly against the responses of immune cells like T cells, APCs, NK cells and NKT cells. It is ideal that this approach be accompanied by the maintenance of Treg cells, thereby facilitating the control of disease for long-term (Croft, 2009). As per these findings several successful endeavors have been made to target these ligand-receptor interactions for the therapeutic management of inflammatory/autoimmune conditions (Gillett *et al*., 2010). Cytokine therapy is an emerging and promising treatment regimen as are the other ones like monoclonal antibodies, avian egg antibodies, gene silencing, gene therapy, apoptins, herbal and panchgavya elements (Mahima *et al*., 2012; Deb *et al*., 2013; Dhama *et al*., 2005a, b; 2013).

Certain catabolic effects on fat cells and whole animals are exerted by TNF-β and have been proven by TNF-α messenger RNA expression profiling in rodent models (obese fa/fa rats) wherein an increase in the uptake of glucose in response to insulin peripherally has been observed significantly (Hotamisligil *et al*., 1993). As TNF-α bears a neuro-inflammatory domain in the nervous system it plays a pivotal role in drug development in the treatment of neuropathic pain originating both centrally and peripherally. It has been proven by various studies conducted in animal models of neuropathic pains based on various types of nerve injuries viz. peripheral versus spinal nerve as well as ligation versus chronic constrictive injury (Leung and Cahill, 2010).

Preclinical studies have analyzed the activity of neutralizing antibodies that are targeting specifically for TNF ligand proteins, or of Fc fusion proteins with a TNFR that binds to the ligand and thereby blocks the endogenous interaction. The effects of blocking the TNF ligand-receptor interactions discuss have been assessed in models of inflammatory disease (viz., allergy, bronchial asthma, organ transplantation, graft-versus-host disease (GvHD) and atherosclerosis) and autoimmune disease (including experimental autoimmune encephalomyelitis (EAE), diabetes, colitis, adjuvant- or collagen-induced arthritis and systemic lupus erythematosus (Taylor *et al*., 2002). These studies have shown that neutralizing any one of these TNF-TNFR interactions can result in overpowering of conditions, which in most of the cases, is precisely linked to decline in CD4+ or CD8+T cells activity, or in other cases results in the impairment of NK- and NKT-cell function (Zimmerer *et al*., 2012).

TNF-β is a tumor promoter helping to produce the toxic effects involved in conventional cancer therapy viz. cytokine release syndrome as well as nephrotoxicity induced by cisplastin. TNF-β antagonists have been developed effectively against rheumatoid arthritis and inflammatory bowel disease due to the central role played by TNF-β in inflammation (Szlosarek and Balkwill, 2003). Inhibition of TNF has also been proven to be an effective therapy for inflammatory diseases viz. psoriasis and psoriatic arthritis; ankylosing spondylitis but the efficacy of preventing septic shock and acquired immunodeficiency syndrome (AIDS) have been questioned. Certolizumab pegol is a novel TNF inhibitor (Esposito and Cuzzocrea, 2009). Different therapeutic agents are now in market under the label of TNF blockers. This includes monoclonal antibodies to TNF and TNF receptor fusion proteins. Drugs named Infliximab and Adalumimab are among the monoclonal antibodies to TNF whereas Etanercept and Lenercept are the TNFR fusion proteins (Gillett *et al*., 2010; Croft, 2009; Croft *et al*., 2012). Etanercept comes under a human recombinant protein which is soluble in nature. It is a fusion protein in which TNFR2 has been coupled with the Fc portion of immunoglobulin G. Infliximab is a chimera of human and murine immunoglobulin G1 monoclonal anti-TNF antibody. Adalibumab is produced by the phage display and is a human anti-human TNF antibody (Bradley, 2008; Gillett *et al*., 2010). In case of rheumatoid arthritis condition all the above drugs have shown to be effective. For patients with Crohn's disease, infliximab is shown to be effective in inducing remission but not etanercept (Tracey *et al*., 2008; Bradley, 2008). In ankylosing spondylitis condition, both etanercept and infliximab are proven to be effective. Various clinical trials have shown that infliximab, etanercept and adalimumab are operative for treating all the manifestations in case of psoriasis. In case of patients affected with refractory asthma has shown evidence for beneficial effects of the drug etanercept on markers of asthma to control the condition (Tyring *et al*., 2007; Tracey *et al*., 2008; Bradley, 2008; Gillett *et al*., 2010; Croft *et al*., 2012).

CONCLUSION

An array of TNFR and TNFL pairs of this superfamily are correlated with their actions in augmenting the ongoing inflammatory function and autoimmune

conditions. These interactions were found to exert several properties on conventional CD4 T cells, CD8 T cells, NK cells and NKT cells, including the stimulation of division, proliferation, survival, differentiation and regulating of cytokine production. Along with this, these interactions furthermore modulate the differentiation, proliferation and activity of regulatory T cells. They target intracellular signaling mediators that control canonical and non-canonical various transcription factors like NF-κB, PI3K/Akt and also calcium/NFAT pathways. They can also promote signals in APCs and non-lymphoid cells that are not yet defined but likely control production of pro-inflammatory cytokines. There are still inordinate gaps in our understanding and scientific facts concerning the activity, expression, downstream signaling pathway and participation of different molecules of TNF superfamily at various platforms of the immune response and over the progression of autoimmune as well as inflammatory diseases. Essentially it is to be resolved that upto what extent these receptors exhibit similarity or dissimilarity among one another in relation to their signalling complexes, difference in cellular responses and disease progression. Upon focusing to the therapy, it is still not well established that which ligand-receptor pair will be the best target for each particular disease conditions. In addition to this, various successful preclinical studies have been conducted in murine models which need their translation to corresponding human conditions. By playing a pivotal role in the cytokine mediator system both peripherally and centrally TNF superfamily certainly has become titan in researches concerning neurological disorders and will make it easier for researchers and scientists to develop various kinds of novel drugs in near future.

REFERENCES

Al-Lamki, R.S., J. Wang, P. Vandenabeele, J.A. Bradley and S. Thiru *et al*., 2005. $TNFR_1$-and $TNFR_2$- mediated signaling pathways in human kidney are cell type-specific and differentially contribute to renal injury. FASEB J., 19: 1637-1645.

Al-Lamki, R.S., T.J. Sadler, J. Wang, M.J. Reid and A.Y. Warren *et al*., 2010. Tumor necrosis factor receptor expression and signaling in renal cell carcinoma. Am. J. Pathol., 177: 943-954.

Arnett, H.A., J. Mason, M. Marino, K. Suzuki, G.K. Matsushima and J.P. Ting, 2001. TNFα promotes proliferation of oligodendrocyte progenitors and remyelination. Nat. Neurosci., 4: 1116-1122.

Ashkenazi, A. and V.M. Dixit, 1998. Death receptors: Signaling and modulation. Science, 281: 1305-1308.

Bach, E.A., M. Aguet and R.D. Schreiber, 1997. The IFN-γ receptor: A paradigm for cytokine receptor signaling. Annu. Rev. Immunol., 15: 563-591.

Balkwill, F., 2006. TNF-β in promotion and progression of cancer. Cancer Metastasis Rev., 25: 409-416.

Behrendt, A.K. and G. Hansen, 2010. CD27 costimulation is not critical for the development of asthma and respiratory tolerance in a murine model. Immunol. Lett., 133: 19-27.

Bradley, J.R., 2008. TNF-mediated inflammatory disease. J. Pathol., 214: 149-160.

Castro, J.E., J.A. Listman, B.A. Jacobson, Y. Wang and P.A. Lopez *et al*., 1996. Fas modulation of apoptosis during negative selection of thymocytes. Immunity, 5: 617-627.

Chang, J.H., Y.S. Ryang, T. Morio, S.K. Lee and E.J. Chang, 2004. *Trichomonas vaginalis* inhibits proinflammatory cytokine production in macrophages by suppressing NF-kappaB activation. Mol. Cells, 18: 177-185.

Chaudhari, U., P. Romano, L.D. Mulcahy, L.T. Dooley, D.G. Baker and A.B. Gottlieb, 2001. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: A randomized trial. Lancet, 357: 1842-1847.

Chauhan, R.S. and K. Dhama, 2008. Cowpathy in induction of cytokines and its importance in control of human and animal diseases. Ibid, Souvenir, pp: 117-121

Clark, J., P. Vagenas, M. Panesar and A.P. Cope, 2005. Structural and functional footprints of the tnf/tnf-r superfamily. Ann. Rheum. Dis., 64: iv70-iv76.

Croft, M., 2003a. Co-stimulatory members of the TNFR family: Keys to effective T-cell immunity? Nat. Rev. Immunol., 3: 609-620.

Croft, M., 2003b. Costimulation of T cells by OX40, 4-1BB and CD27. Cytokine Growth Factor Rev., 14: 265-273.

Croft, M., 2009. The role of TNF superfamily members in T-cell function and diseases. Nat. Rev. Immunol., 9: 271-285.

Croft, M., 2010. Control of immunity by the TNFR-related molecule OX40 (CD134). Annu. Rev. Immunol., 28: 57-78.

Croft, M., W. Duan, H. Choi, S. Eun, S. Madireddi and A. Mehta, 2012. TNF superfamily in inflammatory disease: Translating basic insights. Trends Immunol., 33: 144-153.

Darnell Jr., J.E., 1997. STATs and gene regulation. Science, 332: 1630-1633.

Deb, R., S. Chakraborty, B.M. Veeregowda, A.K. Verma, R. Tiwari and K. Dhama, 2013. Monoclonal antibody and its use in the diagnosis of livestock diseases. Adv. Biosci. Biotechnol.

Dhama, K., R.S. Chauhan and L.K. Singhal, 2005. Anti-cancer activity of cow urine: Current status and future directions. Int. J. Cow Sci., 1: 1-25.

Dhama, K., R. Rathore, R.S. Chauhan and T. Simmi, 2005. Panchgavya: An overview. Int. J. Cow Sci., 1: 1-15.

Dhama, K. and R.S. Chauhan, 2008. Cytokines and the inflammatory responses: An overview. Proceedings of the Compendium of Training cum Workshop on Cytokine, February 26-27, 2008, Mathura, UP., India, pp: 17-33.

Dhama, K., M. Mahendran, R.S. Chauhan and S. Tomar, 2008. Cytokines-Their functional roles and prospective applications in Veterinary practice: A review. J. Immunol. Immunopathol., 10: 79-89.

Dhama, K., A. Hansa and Anjaneya, 2011. Cytokine therapy for animal diseases: The perspectives. Livestock Line, Vol. 4.

Dhama, K., S. Chakraborty, Mahima, M.Y. Wani and A.K. Verma *et al*., 2013. Novel and emerging therapies safeguarding health of humans and their companion animals: A review. Pak. J. Biol. Sci., 16: 101-111.

Dolff, S., D. Quandt, B. Wilde, T. Feldkamp and F. Hua *et al*., 2010. Increased expression of costimulatory markers CD134 and CD80 on interleukin-17 producing T cells in patients with systemic lupus erythematosus. Arthritis Res. Ther., Vol. 12. 10.1186/ar3100

Esposito, E. and S. Cuzzocrea, 2009. TNF-alpha as a therapeutic target in inflammatory diseases, ischemia-reperfusion injury and trauma. Curr. Med. Chem., 16: 3152-3167.

Fang, L., B. Adkins, V. Deyev and E.R. Podack, 2008. Essential role of TNF receptor superfamily 25 (TNFRSF25) in the development of allergic lung inflammation. J. Exp. Med., 205: 1037-1048.

Fousteri, G., A. Dave, B. Morin, S. Omid, M. Croft and M.G. Von Herrath, 2011. Nasal cardiac myosin peptide treatment and OX40 blockade protect mice from acute and chronic virally-induced myocarditis. J. Autoimmun., 36: 210-220.

Francois, R.J., L. Neure, J. Sieper and J. Braun, 2006. Immunohistological examination of open sacroiliac biopsies of patients with ankylosing spondylitis: detection of tumour necrosis factor alpha in two patients with early disease and transforming growth factor beta in three more advanced cases. Ann. Rheumat. Dis., 65: 713-720.

Gabay, C. and I. Kushner, 1999. Acute-phase proteins and other systemic responses to inflammation. N. Engl. J. Med., 340: 448-454.

Galuppo, M., G. Nocentini, E. Mazzon, S. Ronchetti and E. Esposito *et al*., 2011. The glucocorticoid-induced TNF receptor family-related protein (GITR) is critical to the development of acute pancreatitis in mice. Br. J. Pharmacol., 162: 1186-1201.

Geiler, J., M. Buch and M.F. McDermott, 2011. Anti-TNF treatment in rheumatoid arthritis. Curr. Pharm. Des., 17: 3141-3154.

Gillett, A., M. Marta, T. Jin, J. Tuncel and P. Leclerc *et al*., 2010. TNF production in macrophages is genetically determined and regulates inflammatory disease in rats. J. Immunol., 185: 442-450.

Gottlieb, A.B., R. Evans, S. Li, L.M.T. Dooley and C.A. Guzzo *et al*., 2004. Infliximab induction therapy for patients with severe plaque-type psoriasis: A randomized, double-blind, placebo controlled trial. J. Am. Acad. Dermatol., 51: 534-542.

Haritunians, T., K.D. Taylor, S.R. Targan, M.D.M. Dubinsky and M.D.A. Ippoliti *et al*., 2010. Genetic predictors of medically refractory ulcerative colitis. Inflamm. Bowel Dis., 16: 1830-1840.

Hotamisligil, G.S., N.S. Shargill and B.M. Spiegelman, 1993. Adipose expression of tumor necrosis factor-α: Direct role in obesity-linked insulin resistance. Science, 259: 87-91.

Jung, J.H., Y.S. Chae, J.H. Moon, B.W. Kang and J.G. Kim *et al*., 2010. TNF superfamily gene polymorphism as prognostic factor in early breast cancer. J. Cancer Res. Clin. Oncol., 136: 685-694.

Khare, S.D., I. Sarosi, X. Xia, S. McCabe and K. Miner *et al*., 2000. Severe B cell hyperplasia and autoimmune disease in TALL-1 transgenic mice. Proc. Natl. Acad. Sci., 97: 3370-3375.

Kodama, S., M. Davis and D.L. Faustmana, 2005. The therapeutic potential of tumor necrosis factor for autoimmune disease: A mechanistically based hypothesis. Cell. Mol. Life Sci., 62: 1850-1862.

Lange, U., J. Teichmann and H. Stracke, 2000. Correlation between plasma TNFá, IGF-1, biochemical markers of bone metabolism, markers of inflammation/disease activity and clinical manifestations in ankylosing spondylitis. Eur. J. Med. Res., 5: 507-511.

Lee, B.H., S.Y. Park, K.B. Kang, R.W. Park and I.S. Kim, 2002. NF-kappaB activates fibronectin gene expression in rat hepatocytes. Biochem. Biophys. Res. Commun., 297: 1218-1224.

Leung, L. and C.M. Cahill, 2010. TNF-β and neuropathic pain: A review. J. Neuroinflammation, Vol. 7. 10.1186/1742-2094-7-27

Lievens, D., A. Zernecke, T. Seijkens, O. Soehnlein and L. Beckers *et al*., 2010. Platelet CD40L mediates thrombotic and inflammatory processes in atherosclerosis. Blood, 116: 4317-4327.

Locksley, R.M., N. Killeen and M.J. Lenardo, 2001. The TNF and TNF receptor superfamilies: Integrating mammalian biology. Cell, 104: 487-501.

Mahima, A. Rahal, R. Deb, S.K. Latheef and H.A. Samad *et al*., 2012. Immunomodulatory and therapeutic potentials of herbal, traditional/indigenous and ethnoveterinary medicines. Pak. J. Biol. Sci., 15: 754-774.

Mark, K.S., W.J. Trickler and D.W. Miller, 2001. Tumor necrosis factor-á induces cyclooxygenase-2 expression and prostaglandin release in brain microvessel endothelial cells. J. Pharmacol. Exp. Ther., 297: 1051-1058.

Meylan, F., Y.J. Song, I. Fuss, S. Villarreal and E. Kahle *et al*., 2011. The TNF-family cytokine TL1A drives IL-13-dependent small intestinal inflammation. Mucosal Immunol., 4: 172-185.

Mukhopadhyay, S., J.R. Hoidal and T.K. Mukherjee, 2006. Role of TNFá in pulmonary pathophysiology. Respir. Res., Vol. 7. 10.1186/1465-9921-7-125

Nawashiro, H., D. Martin and J.M. Hallenbeck, 1997. Neuroprotective effects of TNF binding protein in focal cerebral ischemia. Brain Res., 778: 265-271.

Nguyen, Q.T., S.A. Ju, S.M. Park, S.C. Lee, H. Yagita, I.H. Lee and B.S. Kim, 2009. Blockade of CD137 signaling counteracts polymicrobial sepsis induced by cecal ligation and puncture. Infect. Immunity, 77: 3932-3938.

Nolte, M.A., R.W. van Olffen, K.P.J.M. van Gisbergen and R.A.W. van Lier, 2009. Timing and tuning of CD27-CD70 interactions: The impact of signal strength in setting the balance between adaptive responses and immunopathology. Immunol. Rev., 229: 216-231.

Oflazoglu, E., I.S. Grewal and H. Gerber, 2009. Targeting CD30/CD30L in Oncology and Autoimmune and Inflammatory Diseases. In: Therapeutic Targets of the TNF Superfamily, Grewal, I.S. (Ed.). Springer, New York, USA., ISBN-13: 9780387895192, pp: 174-185.

Peters, A.L., L.L. Stunz and G.A. Bishop, 2009. CD40 and autoimmunity: The dark side of a great activator. Semin. Immunol., 21: 293-300.

Pfeffer, K., T. Matsuyama, T.M. Kundig, A. Wakeham and K. Kishihara *et al*., 1993. Mice deficient for the 55 kd tumor necrosis factor receptor are resistant to endotoxic shock, yet succumb to *L. monocytogenes* infection. Cell, 73: 457-467.

Rothe, J., W. Lesslauer, H. Lotscher, Y. Lang and P. Koebel *et al*., 1993. Mice lacking the tumour necrosis factor receptor 1 are resistant to IMF-mediated toxicity but highly susceptible to infection by *Listeria* monocytogenes. Nature, 364: 798-802.

Sands, B.E., F.H. Anderson, C.N. Bernstein, W.Y. Chey and B.G. Feagan *et al*., 2004. Infliximab maintenance therapy for fistulizing Crohn's disease. N. Engl. J. Med., 350: 876-885.

Shu, H.B., W.H. Hu and H. Johnson, 1999. TALL-1 is a novel member of the TNF family that is down-regulated by mitogens. J. Leukocyte Biol., 65: 680-683.

Siddiqui, S., V. Mistry, C. Doe, S. Stinson, M. Foster and C. Brightling, 2010. Airway wall expression of OX40/OX40L and interleukin-4 in asthma. Chest, 137: 797-804.

Sumi, T., W. Ishida, A. Ojima, M. Kajisako, T. Sakanishi, H. Yagita and A. Fukushima, 2008. CD27 and CD70 do not play a critical role in the development of experimental allergic conjunctivitis in mice. Immunol. Lett., 119: 91-96.

Sun, X., H. Yamada, K. Shibata, H. Muta and K. Tani *et al*., 2010. CD30 ligand is a target for a novel biological therapy against colitis associated with Th17 responses. J. Immunol., 185: 7671-7680.

Sun, X., S. Somada, K. Shibata, H. Muta and H. Yamada *et al*., 2008. A critical role of CD30 ligand/CD30 in controlling inflammatory bowel diseases in mice. Gastroenterology, 134: 447-458.

Szlosarek, P.W. and F.R. Balkwill, 2003. Tumour necrosis factor á: A potential target for the therapy of solid tumours. Lancet Oncol., 4: 565-573.

Tansey, M.G. and D.E. Szymkowski, 2009. The TNF superfamily in 2009: New pathways, new indications and new drugs. Drug Discovery Today, 14: 1082-1088.

Taylor, L., M. Bachler, I. Duncan, S. Keen and R. Fallon *et al*., 2002. *In vitro* and *in vivo* activities of OX40 (CD134)-IgG fusion protein isoforms with different levels of immune-effector functions. J. Leukocyte Biol., 72: 522-529.

Thompson, A.E., S.W. Rieder and J.E. Pope, 2011. Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis: A meta-analysis of randomized controlled trials. Arthritis Rheumatism, 63: 1479-1485.

Tizard, I.R., 2004. Cytokines and the Immune System. In: Veterinary Immunology: An Introduction, Tizard, I.R. (Ed.). 7th Edn. Saunders, Pennsylvania, USA., pp: 133-144.

Tracey, D., L. Klareskog, E.H. Sasso, J.G. Salfeld and P.P. Tak, 2008. Tumor necrosis factor antagonist mechanisms of action: A comprehensive review. Pharmacol. Ther., 117: 244-279.

Tracey, K.J. and A. Cerami, 1994. Tumor necrosis factor: A pleiotropic cytokine and therapuetic target. Annu. Rev. Med., 45: 491-503.

Tremelling, M., C. Berzuini, D. Massey, F. Bredin and C. Price *et al*., 2008. Contribution of TNFSF15 gene variants to Crohn's disease susceptibility confirmed in UK population. Inflamm. Bowel Dis., 14: 733-737.

Tyring, S., K.B. Gordon, Y. Poulin, R.G. Langley, A.B. Gottlieb, M. Dunn and A. Jahreis, 2007. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. Arch Dermatol., 143: 719-726.

Watkins, L.R., S.F. Maier and L.E. Goehler, 1995. Immune activation: The role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain, 63: 289-302.

Wolfe, F. and K. Michaud, 2004. Heart failure in rheumatoid arthritis: Rates, predictors and the effect of anti-tumor necrosis factor therapy. Am. J. Med., 116: 305-311.

Yang, J., Y. Chu, X. Yang, D. Gao and L. Zhu *et al*., 2009. Th17 and natural Treg cell population dynamics in systemic lupus erythematosus. Arthritis Rheum., 60: 1472-1483.

Zhang, J., X. Wang, H. Fahmi, S. Wojcik and J. Fikes *et al*., 2009. Role of TL1A in the pathogenesis of rheumatoid arthritis. J. Immunol., 183: 5350-5357.

Zhang, Z., W. Zhong, D. Hinrichs, X. Wu and A. Weinberg *et al*., 2010. Activation of OX40 augments Th17 cytokine expression and antigen-specific uveitis. Am. J. Pathol., 177: 2912-2920.

Zimmerer, J.M., P.H. Horne, L.A. Fiessinger, M.G. Fisher, T.A. Pham, S.L. Saklayen and G.L. Bumgardner, 2012. Cytotoxic effector function of CD4-independent, CD8+ T cells is mediated by TNF-β/TNFR. Transplantation, 94: 1103-1110.