## *Review Article*

# Roles of tumor necrosis factor-αand tumor necrosis factor-α receptor 2 in inflammation-related diseases


**Abstract**

The aim of the present review is to provide basic knowledge about the role of tumour necrosis factor-α 1 and tumor necrosis factor-α receptor 2 in neuro Inflammation diseases. We performed an open-ended, English restricted search of PubMed, Embase, PsychINFO, Web of Science, Scopus, and the Cochrane Library for available literature from 24Feb. 2018–12 Oct. 2020, using terms related to neuroinflammation, tumour necrosis factor-alpha, tumour necrosis factor II (TNFR-II), TNF-α and related diseases, TNFR-II and inflammation-related diseases, their relationships, and polymorphism.The main outcomes assessed were the presence of plaques and tangles, behaviour and cognition, reduction in brain tissue mass, and synaptic function the majority of studies were documented a beneficial effect in other areas, including the presence of plaques and tangles and synaptic function. The human studies were showed that TNF-αI was beneficial to Alzheimer's disease patients, with one being a small pilot study and the latter being an observational study, with a high risk of bias. It is concluded that the functions and mechanisms of TNF-α and TNFR-II in inflammation-related diseases will provide new viewpoints and theories in the development and treatment of these diseases.They play important roles in the pathogenesis of diseases induced by or related to inflammatory cytokines and signaling pathways.



**Keywords:**Genetic polymorphisms,Inflammation-related diseases,Tumor necrosis factor-α,Tumor necrosis factor-α receptor 2


## Introduction

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**The role of neuroinflammation in neurodegenerative diseases**

The brain is our most precious organ of our body. Our thoughts, emotions, our ability to reason and communicate with the outside world are all in danger if something damages our brain. In 20th century, Life is stressful, because most people are struggling to keep up and are living with tiredness, anxiety, stress, depression and sleeping problems as a result. Some people tip over the edge into mental health problems from attention deficit disorder to Alzheimer's disease and other dementias. In fact, there's been a massive increase in the incidence of mental health problems in the world. Therefore, protecting our brain has definitely become a priority.

Age-related cognitive declines have been linked to free radical-induced oxidative brain damage. This common enemy has been strongly implicated in variety of diseases that wreak devastating damage on the brain and nerves, known as neurodegenerative diseases.The degeneration of the central nervous systems have characterized by chronic progressive loss of functions as well asstructure of neuronal materials and resulted mental and functional impairments (Campbell et al., 1999). However, the causes due to neuronal degeneration remainsunclear, but some reports indicated that incidence of neuro-degeneration, increases with age (Hof and Mobbs, 2010). Those which affect elder individuals have caused the diseases such as Alzheimer's disease, Motor neuron diseases multiple sclerosis, Amyotrophic lateral sclerosis, Parkinson's disease (PD) (Przedborski et al., 2003; Chen et al., 2016).

**Depression and neuroinflammation**

Normal aging has related to enhancethe expression level of systemic inflammatory factorsviz., pro-inflammatory cytokines (Bruunsgaard et al., 2001; Fagiolo et al., 1993). In the brain, this age-associated inflammation manifests initially as the chronic activation of parenchymal and perivascular macrophage,whichexpressing the pro-inflammatory cytokines as well as increased number of astrocytes (Johnson et al., 1999), that contribute to increase the vulnerability of neuropsychiatric disorders (Capuron et al., 2008). In obese women, the inflammation state was linked with a

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higher concentration of pro-inflammatory cytokines, IL-6, adipokines and CRP (Ouchi et al., 2011). These pro-inflammatory cytokinescorrelated with the symptoms of anxiety and depression (Capuron et al., 2011). Anxiety was alleviated with the surgical removal of fat tissue and reduction of inflammation (Cancello et al., 2005). In agreement with previous studies that the metabolic diseases (obesity, hypertension) have prevalent risk factors of cognitive dysfunction dementia, and depression (McCrimmon et al., 2012), and there hasincreased risk of aging-related diseases that affecting the neuroendocrine,cerebrovascular, cardiovascular, and immune systems in patients suffering major depression (Wolkowitz et al., 2010).

The putative mechanism related to depression and inflammation involved prominent pro-inflammatory cytokines (IL-6 and IL-8), hyperglutamatergiaand endothelial nitric-oxide synthase uncoupling and oxidative stress (Baune et al., 2012). However,thebiological mechanism of depression was still unclear but conventional antidepressant treatments to one-third of depressed patients were unsuccessful, due to the inflammation that contributed to treatment resistance (Rush et al., 2006). In addition, indirect proof of neurovascular dysfunction have been found in major depressive disorder (MDD),which is a severe psychiatric illness and linked with enhances the expression level of inflammatory markers in depression,periphery, and mortality (Kessler et al., 2005; Zunszain et al., 2012). Thereafter, inflammatory markers were recognized in neurodegenerative diseases such as adhesion molecules, MDD cover chemokines, and acute phase proteins (Papakostas et al., 2013).

**Psychiatric illness and neuroinflammation**

Biological abnormalities are highly recognizedin patients with psychiatric disorders, the distinction between psychiatric illness fades and neurological. Separation of psychiatric disorders and neurological were supported by Descartes's conception of the 'mind' as by the reproducibility of neuropathological abnormalities and an ontologically distinct entity (Kendler et al., 2012). Since then, an expanding collection of reproducible biological causes, such ashead trauma, neurosyphilis, demyelination

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stroke, tumor, and many others caused symptoms that overlapped with classic psychiatric disorders (Leboyer et al., 2012). Recently, patients with classical psychiatric disorders, both immunological abnormalities and neuroinflammatory have been documented.

Peripheral immune modulators can induce psychiatric symptoms in human and animal models. The pro-inflammatory IL-1β and tumor necrosis factor alpha (TNF-α) cytokines was injected in healthy animals with demonstrate 'sickness behavior' related with social withdrawal (Harrison et al., 2009; Dantzer et al., 2008). More than 45% of cancer patients treated with IFN-α and non-depressed hepatitis C was reported to develop depressive symptoms linked with increased serum IL-6 levels (McNally et al., 2008). Medical conditions associated with immunological abnormalities and chronic inflammatory viz., rheumatoid arthritis, diabetes, obesity, multiple sclerosis, and malignancies have risk factors for bipolar disorder and depression (Laske et al., 2008). The positive correlation between psychiatric illness and these medical conditions havesuggested the presence of a widespread underlying inflammatory process that affecting the brain and other organs (Raison et al., 2013).

Peripheral humoral and cellular immunological abnormalitiesare more widespread in psychiatric patients as compare to healthy one. In both replication studies (n = 36 MDD, n = 43 healthy controls) and pilot (n = 34, major depressive disorder (MDD) and, comprising nine serum biomarkers which reported to distinguished MDD subjects from healthy controls with 81.3% and 91.7% sensitivity (Benros et al., 2011; Steiner et al., 2012).

**Role of tumor necrosis factor in Neuroinflammation**

The tumor necrosis factor (TNF)was initially discovered in 1975 by a team of scientists in the study of hemorrhagic necrosis (Carswell et al., 1975). It was named by its function which can lead to lysis in tumour cells. After its discovery, numerous studies have indicated that TNF is an important cytokine involved in pathological and

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physiological processes, especially associated withinflammation, such as acute inflammation, autoimmune disease, tumour-associated inflammation (Chu, 2013). Tumor necrosis factor-alpha (TNF) is an extremely pleiotropic cytokine, which occurs in transmembrane and a soluble form.Tumor necrosis factor-alpha is mainly produced by immune cells upon contact with danger associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), but can be induced in macrophages, microglia, endothelial cells and lymphocytes (Ramseyer et al., 2013). It is a functional homotrimer transmembrane protein with molecular weight of 26-kDa (Speeckaert et al., 2012). There are two forms of TNF-α in vivo, one is the membrane-bound form (mTNF-α) while another is the soluble form (sTNF-α) (Hehlgans and Pfeffer, 2005). Therefore, TNF-α, a type II transmembrane protein in intracellular amino terminus, can activate signaling pathways as a membrane integrated protein or as a soluble cytokine released after proteolytic cleavage (Black et al., 1997). To be more precise, TNF-α is secreted into the extra cellar space by metalloproteinase TNF-α converting enzyme after expression.During the translocation, mTNF-α was sheded into sTNF-α as a functional 17-kDa form (Lorenzen et al., 2011). Although TNF-α was described as an anti-tumorigenic cytokine in the beginning (Carswell et al., 1975).

The major function of TNF-α is to initiate inflammatory responses via activating a variety of proinflammatory cytokines, matrix metalloproteinases, chemokines, and vascular endothelial adhesion molecules which are known to enhance inflammation (Leung, 2013). The function of TNF-α is mediated by two receptors, such as TNF receptor 1 (TNFR1) and TNFR2. The extracellular domains of the both TNF receptors have shares a common structure which is composed of 4 Cysteine-rich domains (CRDs). TNF and its receptors are name-giving for the TNF superfamily (TNFSF) of ligands and the TNFSF ligandbinding receptors of the TNF receptor superfamily (TNFRSF) that included TNFR1 and TNFR2 as two distinct subgroups (Vandenabeele et al., 1995). TNFR1 has a death domain in its cytoplasmic part and interacts with DD-containing proteins that enable a activation of cytotoxic signaling and

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proinflammatory pathways. In contrast, TNFR2 recruits the adapter protein TNF receptor-associated factor 2 (TRAF2) and activates the alternative NFκB pathway but the mechanism is still unclear (Pegoretti et al., 2018).TNFR-I and TNFR-IIcan activate different signaling pathways. The activation of TNFR-I signaling pathway induces the cascade related to apoptosis,the cell nature,and the condition of cell activation as well as the cell cycle (Micheau and Tschopp, 2003). However, TNFR-II signalstrigger cell survival pathways predominantly in the stimulated T cells which as a source of cell proliferation (Aggarwal, 2003). Therefore, they are two distinct receptors and can be involved in different physiological or pathological processes. For instance, TNFR-I is mainlyassociated with neurodegeneratiion, whereas TNFR-II is involved in neuroprotection and tissue regeneration (Fischer et al., 2011). Moreover, increasing evidence has shown that activation of TNF-α signaling pathway is associated with inflammatory diseases (Abdallah et al., 2015; O'Donovan et al., 2015).TNF fulfills manifold functions in a variety of immune regulatory processes that are considerable relevance to patho-physiological situations arising from sterile tissue damage-induced inflammation or pathogen. Therefore, the current review aimed at the brief summary of relationships between TNF-α and TNFR-II and related diseases or their genetic variations. Understanding these associations and possible functions of TNF-α and TNFR-II involved in will promote future research on the molecular mechanism and treatment of diseases related with inflammation-related diseases, including psychiatric disorders.

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## Materials and Methods

### Literature search

We performed an open-ended, English restricted search of Web of Science, PubMed, Embase, Scopus, PsychINFO, and the Cochrane Libraryfor available literature from 24Feb. 2018 – 12 Oct. 2020, using terms related to neuroinflammation, tumour necrosis factor-alpha, and tumour necrosis factor II (TNFR-II), association between TNF-α and

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related diseases and association between TNFR-II and inflammation-related diseases, their relationships and polymorphism, and clinical implications and limitations. .

**Inclusion/exclusion criteria**

In this review, the selected studies were included with the following criteria: report original work,published in a peer-reviewed journal, research conducted on human participantsoranimal subjects, the animal studies were includedanon-transgenic or transgenic models of AD, or human participants which was diagnosed with AD through an administration of a TNF-αI or a genetic intervention leading to ablation of the TNF receptor (TNFR). In addition, case studies, and unpublished dissertations or theses,conference, research protocols, cell cultures studies were excluded.

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**Quality assessment of methodology**

The included studies were assessed by two blind, independent raters (J. E. and G. R.), with any discrepancies in ratings being resolvedthrough discussion with an independent reviewer (R. G.).

**Results and Discussion**

**Association between TNF-α and diseases**

Inflammationisa physiological process, which repairs tissues in response to exogenous or endogenous aggressions, which may lead to detrimental consequences. As a protein involved in inflammation process, TNF-α has been identified asakey role in the inflammatory neurological disorders,such as elderly with increased risk of morbidityand mortality have had the higher TNF-α level compared with controls (Michaud et al., 2013). Moreover, asTNF-α is able to cause increased muscle catabolism, increased plasma TNF-α concentration has been shown to be related to the reduced physical performance, decreased muscle strength, and reductive muscle mass (Langen et al., 2004). In patients with mild Alzheimer disease elevated plasma TNF-α

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levels were found when compared to healthy controls, suggesting the possible role of TNF-α in the pathophysiology of neurodegenerative disorders (Fillit et al., 1991).

As for the mental diseases, available evidences also proposed a positive relationship betweenposttraumatic stress disorder (PTSD) and immune dysfunction which could be induced by TNF-α (Jergović et al., 2014). A study about subjects with PTSD in Croatia indicated middle-aged subjects with PTSD had shorter telomere length of peripheral blood mononuclear cells than their healthy counterparts because of changes in immune activity such as increased levels of TNF-α, indicating changes of immune reactivity, including TNF-α production can affect mental health (Lindqvist et al., 2014). TNF-α is not only related to PTSD, but also associated with major depressive disorder (MDD). As a mental disease with an incidence of up to 20% in general population, a meta-analysis reported a significantly increased TNF-αlevel in the subjects with MDD when compared with non-depressed controls. However, another study in MDD females aged from 20-55 years indicated there was no statistically significant different of TNF-α level between depressive subjects and controls, resulted from the unstable of TNF-α (Grassi-Oliveira et al., 2009). Taking into account of the contradictory reports on the relationship between TNF-α with depression, future studies should take possible mechanisms related with immune dysregulation and abnormal inflammatory response in the depression development into consideration to clarify the role of TNF-α in depression. Moreover, TNF-α has been approved to collaborate with its receptors, such as TNFR-II, to affect the development of diseases (Polz et al., 2014).

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**Structure of TNFR-II and its signaling**

Although the affinities of both TNFR-I and TNFR-II for sTNF-α are very similar, unlike TNFRI with a cytoplasmic death domain in its structure, TNFR-II is unable to active the apoptosis due to the lack of death domain (Aggarwal, 2003). Moreover, TNFR-II is mainly located on the plasma membrane in the epithelial cells, oligodendrocytes, myocytes, T lymphocytes, cardiomyocytes or stem cells, whereas TNF-RI is detected almost all kinds of cells and is typically localized in the Golgi

apparatus (Wang et al., 2013). Due to the different locations in vivo and different structures, TNF can result in inflammation and tissue injury by bind with TNFR-I, while increasing evidence has indicated its critical roles in inflammation-related processes via the activation of TNFR-II (Fuchs et al., 1992). In general, TNFR-II is more efficiently activated by mTNF-α than by sTNF-α. Meanwhile, TNFR-II can co-stimulate and enhance their activation to T-cell receptor (TCR)-mediated signaling [Fig. 1] (Chen and Oppenheim, 2011).

TNFR-II gene, also known as *CD120b*, or *TNF-R P75/80*, comprises 9 introns and 10 exons in its sequence and sits on chromosome 1p36.3-p36.2 (Benjafield et al., 2001). TNFR-II is a 74kDa type I transmembrane glycoprotein which can orchestrate the complex biological functions of TNF-α (Chen and Oppenheim, 2011). Initially, TNFR-II was thought be to the protein that mediate and support the TNFR-I in the process named ligand passing (Tartaglia et al., 1993). However, after further clarification of characteristics in the signaling pathways activated by the binding of TNF-α and different receptors, TNFR-II was exhibited an enhanced ability to bind with mTNF-α as sTNF has a tight trimer structure which is unable to be released by the receptor. In the structure of TNFR-II, there is an intracellular domain which can recruit cytosolic proteins via the conformational changes induced by extracellular signals binding (Ledgerwood et al., 1999). TNFR-associated factor 2 (TRAF2), with the ability to contacts the TNFR-II directly, is one of the cytosolic protein that recognized by the extracellular signal bound TNFR-II (Fotin-Mleczek et al., 2002). By recruitments of TRAF2, TNFR-II has the potential to activate cIAP1 and cIAP2 which are cellular inhibitors of apoptotic proteins (Rothe et al., 1995). In primary cells with expression of TNFR-II, although the specific role of cIAP1 in TNFR-II mediatedsignaling pathway, cIAP1 has been identified to regulate the duration of TNF signaling because of its ubiquitin protein ligase activity (Zhao et al., 2007). However, the study indicated that only over-expressed TNFR-II can exhibit significant activation of NFκB while physiological levels of TNFR-II failed to induce NFκB activation (Jupp et al., 2001).

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Therefore, TNFR-II seems to be only a weak trigger for NFκB activity although it has high combination ability with TRAF2. The contradiction between the low NFκB activation ability and the high TRAF2 binding capability of TNFR-II might be resulted from the block of signals from the conventional TRAF2 binding site (T2bs-N) of a carboxyl-terminal TRAF2-binding site (T2bs-C) (Grech et al., 2005). On the contrary, a study on the *rip*$^{-/-}$ mice (lacking RIPK1) indicated that TNFR-II has the ability to activate NFκB by mediating the degradation of IκBα (Mak and Yeh, 2002). Taken together, TNFR-II signaling induced by TNFR2 binding may result in NFκB activation in certain cell types. After NFκB activation, TNFR-II signaling can induce differentiation; cytokine production, apoptosis, as well as cell death in T lymphocytes via the NFκB transcribes (Pimentel-Muiños et al., 1999). The mechanism involved in the TNFR-II induced cell death might be related to necroptosis resulting from the prevention of phosphatidylinositol 3 kinase (PI3K) by TNFR2 activation (Leung, 2013). Contrarily, TNFR-II has the potential to activate PI3K and Akt by the stimulation of epithelial/endothelial tyrosine kinase (Etk) to bring about cell proliferation and survival (Al-Lamki et al., 2010). The role of TNFR-II in immune systemisreflected by a not so well characterized immature subpopulation of myeloid cell, the myeloid-derived suppressor cells (MDSC) (Zhao et al., 2012). Both maturation and optimal suppression of MDSCappeartodepend onactivation of TNFR-II (Polz et al., 2014). Due to the complexity in TNFR-II signaling pathways, a more understanding of TNFR-II could leads to discuss its beneficial implications.

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**Association between TNFR-II and inflammation-related diseases**

As a critical protein in the TNF-α induced signaling pathway, increasing evidence has proved the relationship between TNFR-II and inflammation-related diseases. In fact, the previous study insisted TNFR-II was a more reliable biomarker of inflammation because of its higher stability than TNF-α (Kronfol and Remick, 2000). For example, as the strong associations among obesity, inflammation and vascular condition, TNFR-II was indicated to be related with coronary heart disease and other metabolic diseases

(Das, 2001; Warner and Libby, 1989). Another study in 1300 non-diabetic subjects from the prospective Hong Kong Cardiovascular Risk Factor Prevalence Study (CRISPS) also indicated TNFR-II, together with adiponectin, had the potential to be a risk factor for prediction of diabetes in Chinese population (Shai, 2005). Meanwhile, Wang et al. (2013)analyzed the data from adult male mice with TNFR-II(-/-) and indicated that TNFR-II deficiency could exacerbate adiponectin expression suppression by enhancing a transcriptional factor ATF3, which might be a trigger of cardio diseases. Increased plasma TNFR-II levels was alsoassociated with incidentfuture intra-cerebral hemorrhage in Malmö Diet and Cancer Study (n=28 449) as its relationship with inflammation (Woo et al., 2012; Wang et al., 2013).

Not only the cardiovascular diseases and metabolic diseases, TNFR-II contributes to other inflammation-related diseases, such as cancer. Previous study in vitro have demonstrated the significant association between TNFR-II with acute cellular rejection (Civic et al., 2000) and clear cell renal carcinoma (ccRCC) by its role in regulation cellular responses (Wang and Al-Lamki, 2013). The study about the anti-inflammatory therapeutic potentialof TNFR-II in mice had indicated that TNFR-II activation had the potential to be a therapeutic strategy in autoimmune arthritis as TNFR-II induced elevation of regulatory cell types and symptomatic relief of arthritis (Lamontain et al., 2019). In the study of human colon interstitial fibroblast cell line CCD-18Co, TNFR-II induced AKT and ERK signaling pathways had shown the ability to activate colorectal cancer fibroblasts in microenvironment via abrogate downregulation of Ki67, FAP and α-SMA expressions effectively (Wang et al., 2017).

Actually, TNFR-II also plays an important role in the morbidity and development ofpsychiatric disorders, which may be also related to inflammation. For example, deletion of TNFR-II together with TNFR-I in the mice would lead to anxiolytic-like effects, as well as an absence of aggressive behavior, suggesting the association between TNFR-II and anxiety as TNFR-II modulation in brain regions about these behaviors (Patel et al., 2010). Another similar study also demonstrated that mice with

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absence of TNFR-II could result in an antidepressant-like response in the test of forced swim, and a hedonic response in a sucrose drinking test compared with their wild type counterparts (Simen et al., 2006). Furthermore, Gimsa et al. (2012), has found significantly higher corticosterone levels were observed in *TNFR-II* knockout mice after social disruption (SDR) than control mice, suggesting anxiety-like behaviour and corticosterone responses of TNFR-II. The decreased volume of hippocampal induced by increased inflammation have been identified to be related with PTSD, and the study of 246 Gulf War veterans found that hippocampal volume was negatively associated with TNFR-II levels. Meanwhile, in the above study, the severity of PTSD had shown to be positively associated with TNFR-II levels, suggesting the importance of TNFR-II in the incidence and development of PTSD (O'Donovan et al., 2015). On the other hand, abnormal expression of TNFR-II in the lymphocytes was observed in 31 patients with MDD, and there was a significant elevation of serum TNFR-II level in MDD patients (Rizavi et al., 2016). Another study of stable heart failure patients showed that there was a relationship between sTNFR-II levels and the degree of depression in the subjects with depression even after adjusting of age, body mass index and other factors related to heart failure (Moughrabi et al., 2014).

**Polymorphisms of *TNF-α* and *TNFR-II* and their relationships with inflammation-related diseases**

Many Studies described about the different genetic variations of *TNF-α* have the potential to be involved in several inflammation-related diseases due to the changes in function or expression of *TNF-α* (Hajeer and Hutchinson, 2001). Plenty of studies about the genetic polymorphisms of *TNF-α* and ischemic heart disease (IHD) have stated the IHD risk was associated with TNF-α -238G/A (rs361525), -308G/A (rs1800629), -1031T/C (rs1799964) and other polymorphisms of *TNF-α* respectively (Bennet et al., 2006; Hou et al., 2009). Moreover, another study in human immunodeficiency (HIV)-hepatitis C (HCV) virus co-infected patients found the 238GG genotype of TNF-α promoter could be an independent factor on the

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developmentof liver cirrhosis (Corchado et al., 2013). A meta-analysis indicated *TNF-α* -857T/C polymorphism could be a possible risk factor to predict susceptibility of hepatocellular cancer (Wang et al., 2016).While TNF-α -850C/T genetic variation was shown to be increased risk of AD (Perry et al., 2001).

As for the psychosocial disease,the current study showed that the higher prevalence of T allele of TNF-RII rs1061622 was found in the depressed female adolescents after the earthquake (Memon et al., 2018).Previous studies have demonstrated that frequency of *TNF-RII* rs1061622 G allele which was a functional amino acid substitution at codon 196 from methionine to arginine is associated with narcolepsy (Hohjoh et al., 2000). Moreover, there were increased frequencies of G allele or genotype of *TNF-RII* rs1061622 patients with paranoid schizophrenia (Thabet et al., 2011). Furthermore, the same genetic variation has been explored in the feasible role in the diagnosis of non-small cell lung cancer (NSCLC) (Guan et al., 2011).

**Clinical implications**

It has been shown that before the development of AD pathology,an increase in synaptic function of glutamatergic neurons occurs that subsequently leading to deleterious effects on cognition. The administration of TNFα-I which was reported byCavanaghetal.reduced the observed abnormalities, for this reason, treatment with TNFα-I beneficial to patients in the initial stages of the disease.

**Strengths and limitations**

The main strengths of the current review was broad range of studies were examined in all the six databases. The main limitation of this review was, it was not possible to statistically analyze the results obtained from the included studies as the sample size was not stated in the vast majority of them. The conclusions were based on only descriptive and lack quantitative synthesis.

**Conclusion**

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TNF-αand its receptor TNFR-II are important proteins which are involved in inflammatory process. They play important roles in the pathogenesis of diseases induced by or related to inflammatory cytokines and signaling pathways. The understanding relationships, functions and mechanisms of TNF-α and TNFR-II in inflammation-related diseases will provide new viewpoints and theories in the development and treatment of these diseases.

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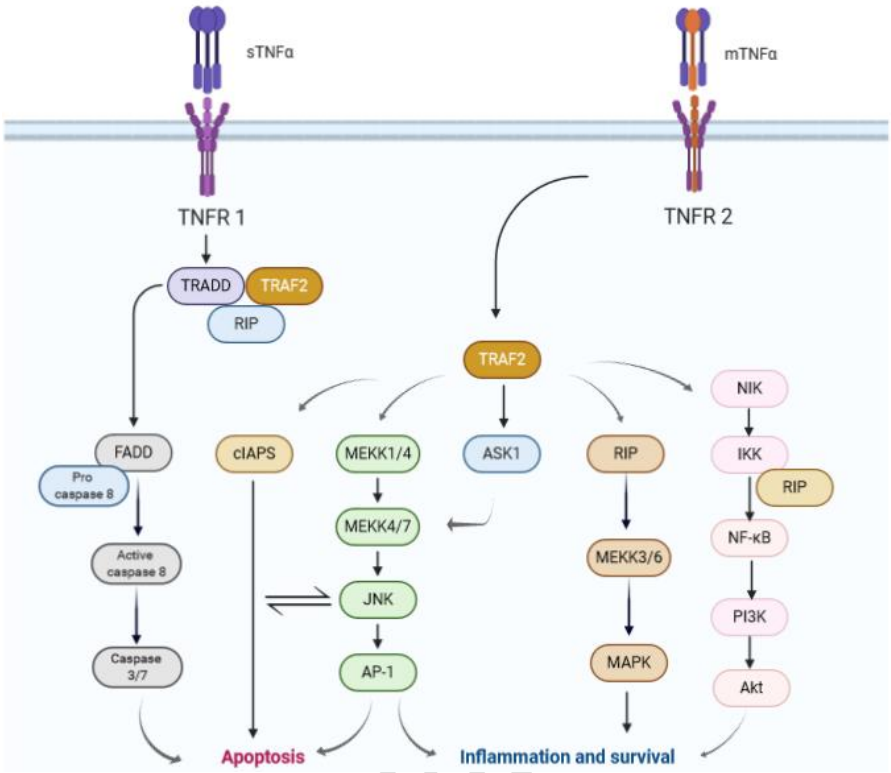


Fig 1: T-cell receptor (TCR)-mediated signaling pathway