Journal of Pharmaceutical Research International

33(52A): 234-245, 2021; Article no.JPRI.76883
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Roles of Tumor Necrosis Factor-α and Tumor Necrosis Factor-α Receptor 2 in Inflammation-Related Diseases

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Authors' contributions

This work was carried out in collaboration among all authors. Authors NHM and AHL developed the research conception and took the initiatives of this review, organizing relevant data, prepare to write and drafted the manuscript. Authors MK and MRM provides greater contribution towards collecting the material. Authors MK, SQA and AHL revised the review paper and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i52A33579
Editor(s):
(1) Dr. S. Prabhu, Sri Venkateswara College of Engineering, India.
Reviewers:
(1) Bushra Jasim Mohammed, University of Baghdad, Iraq.
(2) Özlem Coşkun, Çanakkale Onskiz Mart University, Turkey.
Complete Peer review History, details of the editor(s), Reviewers and additional Reviewers are available here: https://www.sdiarticle5.com/review-history/76883

Review Article

Received 12 September 2021
Accepted 24 November 2021
Published 29 November 2021

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,

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and the Cochrane Library for available literature from 24Feb. 2018–12 May 2021, using terms related to neuroinflammation, tumour necrosis factor-α, 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.

1. INTRODUCTION

1.1 The Role of Neuroinflammation in Neurodegenerative Diseases

The brain is most precious organ of the body. The thoughts, emotions, and ability to reason as well as to communicate with the outside world are all in danger if something damages the 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. There has been a massive increase in the incidence of mental health problems in the world. Therefore, protecting the brain has 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 a variety of diseases that wreak devastating damage on the brain and nerves, known as neurodegenerative diseases. The degeneration of the central nervous system has been characterized by chronic progressive loss of functions as well as structure of neuronal materials and resulted in mental and functional impairments [1]. However, the cause of neuronal degeneration remains unclear, but some reports indicated that the incidence of neurodegeneration, increases with age [2]. Those which affect elder individuals have caused the diseases such as Alzheimer's disease, Motor neuron diseases multiple sclerosis, Amyotrophic lateral sclerosis, and Parkinson's disease (PD) [3,4].

1.2 Depression and Neuroinflammation

Normal aging has been related to enhancing the expression level of systemic inflammatory factors viz, pro-inflammatory cytokines [5,6]. In the brain, age-associated inflammation manifests initially as the chronic activation of parenchymal and perivascular macrophage, which expresses the pro-inflammatory cytokines as well as an increased number of astrocytes [7], that contribute to increasing the vulnerability of neuropsychiatric disorders [8]. In obese women, the inflammation state was linked with a higher concentration of pro-inflammatory cytokines, Interleukin 6 **(**IL-6), and adipokines C - reactive protein (CRP) [9]. These pro-inflammatory cytokines correlated with the symptoms of anxiety and depression [10]. Anxiety was alleviated with the surgical removal of fat tissue and reduction of inflammation [11]. In agreement with previous studies that the metabolic diseases (obesity, hypertension) have prevalent risk factors of cognitive dysfunction dementia, and depression [12,13], and there has increased risk of aging-related diseases that affect the neuroendocrine, cerebrovascular, cardiovascular and immune systems in patients suffering major depression [14,15].

The putative mechanism related to depression and inflammation involved prominent pro-inflammatory cytokines, IL-6 and Interleukin 8 (IL-8), hyperglutamatergia, endothelial nitric-oxide synthase uncoupling, and oxidative stress [16]. However, the biological 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 [17]. In addition, indirect proof of

neurovascular dysfunction has been found in major depressive disorder (MDD), which is a severe psychiatric illness and linked with enhancing the expression level of inflammatory markers in depression, periphery, and mortality [18,19]. Thereafter, inflammatory markers were recognized in neurodegenerative diseases such as adhesion molecules, MDD cover chemokines, and acute phase proteins [20].

1.3 Psychiatric Illness and Neuroinflammation

Biological abnormalities are highly recognized in patients with psychiatric disorders, the distinction between psychiatric illness fades and neurological. The separation of psychiatric and neurological disorders was supported by Descartes's conception of the 'mind' as by the reproducibility of neuropathological abnormalities and an ontologically distinct entity [21]. Since then, an expanding collection of reproducible biological causes, such as head trauma, neurosyphilis, demyelination stroke, tumor, and many other symptoms that overlapped with classic psychiatric disorders [22]. Recently, in patients with classical psychiatric disorders, both neuroinflammatory and immunological abnormalities have been documented.

Peripheral immune modulators can induce psychiatric symptoms in human and animal models. The pro-inflammatory Interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) cytokines were injected in healthy animals with demonstrated 'sickness behavior' related to social withdrawal [23,24]. More than 45% of cancer patients treated with IFN-α and non-depressed hepatitis C were reported to develop depressive symptoms linked with increased serum IL-6 levels [25]. 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 [26]. The positive correlation between psychiatric illness and these medical conditions has suggested the presence of a widespread underlying inflammatory process that affects the brain and other organs [27] (Olawuyi and Raufu 2012).

Peripheral humoral and cellular immunological abnormalities are more widespread in psychiatric patients as compared to the 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 [28,29].

1.4 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 [30]. 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 physiological processes, especially associated with inflammation, such as acute inflammation, autoimmune disease, tumour-associated inflammation [31]. 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 the danger-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) but can be induced in macrophages, microglia, endothelial cells, and lymphocytes [32]. It is a functional homotrimer transmembrane protein with a molecular weight of 26-kDa [33]. 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) [34]. 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 [35]. 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 shed into sTNF-α as a functional 17-kDa form [36]. Although TNF-α was described as an anti-tumorigenic cytokine in the beginning [30].

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 [37]. The function of TNF-α is mediated by two receptors, such as TNF receptor 1 (TNFR1) and TNFR2. The extracellular domains of both TNF receptors have shared 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 ligand-binding receptors of the TNF receptor superfamily (TNFRSF) that included TNFR1 and TNFR2 as two distinct subgroups [38]. TNFR1 has a death domain in its cytoplasmic part and interacts with DD-containing proteins that enable the activation of cytotoxic signaling and proinflammatory pathways. In contrast, TNFR2 recruits the adapter protein TNF receptor-associated factor 2 (TRAF2) and activates the alternative nuclear factor kappa B **(**NFκB) pathway but the mechanism is still unclear [39]. TNFR-I and TNFR-II can 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 [40]. However, TNFR-II signals trigger cell survival pathways predominantly in the stimulated T cells which as a source of cell proliferation [41]. Therefore, they are two distinct receptors and can be involved in different physiological or pathological processes. Moreover, increasing evidence has shown that activation of the TNF-α signaling pathway is associated with inflammatory diseases [42,43]. TNF fulfills manifold functions in a variety of immune regulatory processes that are the considerable relevance to pathophysiological situations arising from sterile tissue damage-induced inflammation or pathogen. Therefore, the current review aimed at a briefed 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 will promote future research on the molecular mechanism and treatment of diseases related to inflammatory diseases, including psychiatric disorders.

2. MATERIALS AND METHODS

2.1 Literature Search

We performed an open-ended, English restricted search of Web of Science, PubMed, Embase, Scopus, PsychINFO, and the Cochrane Library for available literature from 24Feb. 2018 – 12 May 2021, using terms related to neuroinflammation, tumour necrosis factor-alpha, and tumour necrosis factor II (TNFR-II), association between TNF-α and related diseases and an association between TNFR-II and inflammation-related diseases, their relationships and polymorphism, and clinical implications and limitations.

2.2 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 participants or animal subjects. The animal studies were included non-transgenic or transgenic models of AD, or human participants which were diagnosed with AD through an administration of a TNF-α I or a genetic intervention leading to ablation of the TNF receptor (TNFR). In addition, case studies, and unpublished dissertations or theses, conferences, research protocols, cell cultures studies were excluded.

2.3 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 resolved through discussion with an independent reviewer (R. G.).

3. RESULTS AND DISCUSSION

3.1 Association between TNF-α and Diseases

Inflammation is a physiological process, which repairs tissues in response to exogenous or endogenous aggressions, which may lead to detrimental consequences. As a protein involved in the inflammation process, TNF-α has been identified as a key role in inflammatory neurological disorders, such as elderly with increased risk of morbidity and mortality have had the higher TNF-α level compared with controls [44]. Moreover, as TNF-α can cause increased muscle catabolism, increased plasma TNF-α concentration is related to reduced physical performance, decreased muscle strength, and reductive muscle mass [45]. In patients with mild Alzheimer's disease elevated plasma TNF-α levels were found when compared to healthy controls, suggesting the possible role of TNF-α in the pathophysiology of neurodegenerative disorders [46].

As for the mental diseases, available shreds of evidence also proposed a positive relationship between posttraumatic stress disorder (PTSD) and immune dysfunction which could be induced by TNF-α [47]. 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 [48]. TNF-α is not only related to PTSD but is also associated with major depressive disorder (MDD). As a mental disease with an incidence of up to 20% in the 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 difference of TNF-α level between depressive subjects and controls, resulting from the unstable of TNF-α [49]. Considering the contradictory reports on the relationship between TNF-α with depression, future studies should take possible mechanisms related to immune dysregulation and abnormal inflammatory response in the depression development 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 [50].

3.2 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 be active the apoptosis due to the lack of death domain [41]. 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 in almost all kinds of cells and is typically localized in the Golgi apparatus [51]. Due to the different locations in vivo and different structures, TNF can result in inflammation and tissue injury by binding with TNFR-I, while increasing evidence has indicated its critical roles in inflammation-related processes via the activation of TNFR-II [52]. 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] [53].

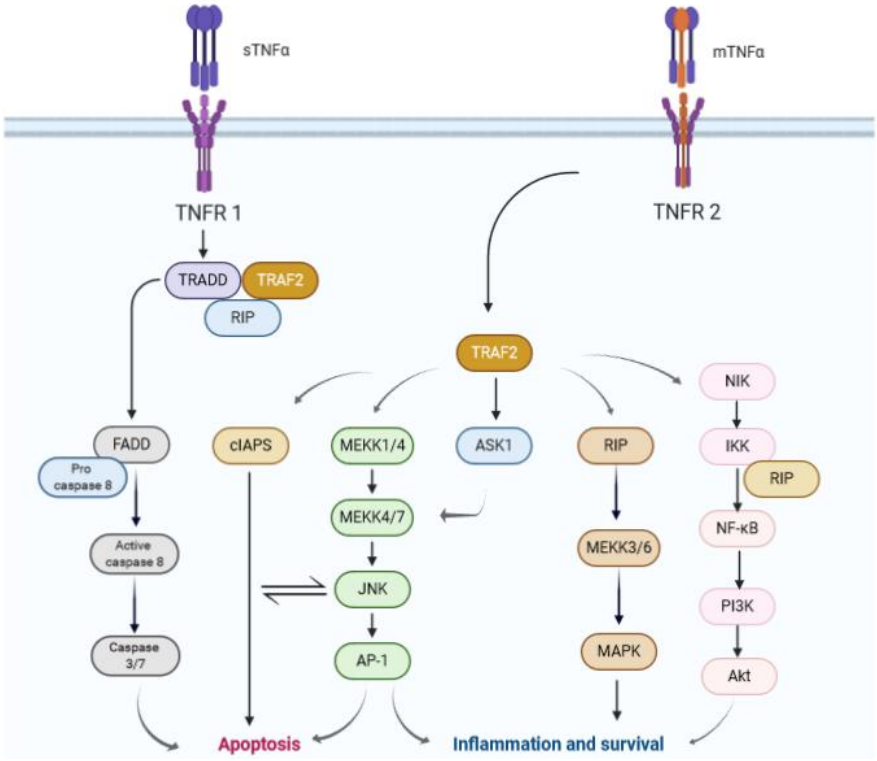

Fig. 1. T-cell receptor (TCR)-mediated signaling pathway

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 [54]. TNFR-II is a 74kDa type I transmembrane glycoprotein which can orchestrate the complex biological functions of TNF-α [53]. Initially, TNFR-II was thought to be the protein that mediates and supports the TNFR-I in the process named ligand passing [55]. 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 that can recruit cytosolic proteins via the conformational changes induced by extracellular signals binding [56]. TNFR-associated factor 2 (TRAF2), with the ability to contact the TNFR-II directly, is one of the cytosolic proteins that recognized by the extracellular signal bound TNFR-II [57]. By recruitments of TRAF2, TNFR-II has the potential to activate cIAP1 and cIAP2 which are cellular inhibitors of apoptotic proteins [58]. In primary cells with expression of TNFR-II, although the specific role of cIAP1 in TNFR-II mediated signaling pathway, cIAP1 has been identified to regulate the duration of TNF signaling because of its ubiquitin-protein ligase activity [59]. 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 [60]. Therefore, TNFR-II seems to be only a weak trigger for NFκB activity although it has a high combination ability with TRAF2. The contradiction between the low NFκB activation ability and the high TRAF2 binding capability of TNFR-II might result from the block of signals from the conventional TRAF2 binding site (T2bs-N) of a carboxyl-terminal TRAF2-binding site (T2bs-C) [61]. On the contrary, a study on the *rip*$^{-/-}$ mice (lacking RIPK1) indicated that TNFR-II can activate NFκB by mediating the degradation of IκBα [62]. 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 [63]. 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 [36]. 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 [64]. The role of TNFR-II in the immune system is reflected by a not so well characterized immature subpopulation of the myeloid cell, the myeloid-derived suppressor cells (MDSC) [65]. Both maturation and optimal suppression of MDSC appear to depend on activation of TNFR-II [50]. Due to the complexity in TNFR-II signaling pathways, a more understanding of TNFR-II could lead to discussing its beneficial implications.

3.3 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. The previous study insisted TNFR-II was a more reliable biomarker of inflammation because of its higher stability than TNF-α [66]. 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 [67,68]. 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 the prediction of diabetes in the Chinese population [69]. Meanwhile, Wang et al. [70] 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 were also associated with incident future intra-cerebral hemorrhage in Malmö Diet and Cancer Study (n=28 449) as its relationship with inflammation [71,51].

Not only the cardiovascular diseases and metabolic diseases, TNFR-II contributes to other inflammation-related diseases, such as cancer. The Previous study in vitro has demonstrated the significant association between TNFR-II with acute cellular rejection [72] and clear cell renal carcinoma (ccRCC) by its role in regulating cellular responses [51]. The study about the anti-inflammatory therapeutic potential of 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 [73]. 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 the microenvironment via abrogating downregulation of Ki67, FAP and α-SMA expressions effectively [74].

TNFR-II also plays an important role in the morbidity and development of psychiatric 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 [75]. Another similar study also demonstrated that mice with the 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 [76]. Furthermore, Gimsa et al. [77], 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 has been identified and related to 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 [43]. 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 [78]. 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 [79].

3.4 Polymorphisms of *TNF-α* and *TNFR-II* and their Relationships with Inflammation-related Diseases

Many Studies described 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 [80]. Plenty of studies about the genetic polymorphisms of TNF-αand 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 [81,82]. 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 development of liver cirrhosis [83]. A meta-analysis indicated *TNF-α* -857T/C polymorphism could be a possible risk factor to predict the susceptibility of hepatocellular cancer [84]. While TNF-α -850C/T genetic variation was shown to be increased the risk of AD [85].

As for psychosocial disease, the current study showed that the higher prevalence of the T allele of TNF-RII rs1061622 was found in depressed female adolescents after the earthquake [86]. Previous studies have demonstrated that the frequency of the *TNF-RII* rs1061622 G allele which was a functional amino acid substitution at codon 196 from methionine to arginine is associated with narcolepsy [87]. Moreover, there were increased frequencies of G allele or genotype of *TNF-RII* rs1061622 patients with paranoid schizophrenia [88]. Furthermore, the same genetic variation has been explored in the feasible role in the diagnosis of non-small cell lung cancer (NSCLC) [89].

4. CLINICAL IMPLICATIONS

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

5. STRENGTHS AND LIMITATIONS

The main strength of the current review was a broad range of studies were examined in all 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 conclusion was based on only descriptive and lack quantitative synthesis.

6. CONCLUSION

TNF-α and its receptors TNFR-II are important proteins that are involved in inflammatory process. They play important roles in the pathogenesis of diseases induced by or related to the 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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