

## R E V I E W

# An Overview of The Role of Tumor Necrosis Factor-Alpha in Epileptogenesis and Its Therapeutic Implications

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**Abstract.** The complex association between neuroinflammation and seizures has been widely investigated in recent years. As mediators of inflammatory response, cytokines like tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) are potential therapeutic targets for epileptic disorders. TNF- $\alpha$  is a pleiotropic cytokine with a controversial role in epileptogenesis, seemingly capable to both favor the genesis of seizures and elicit neuromodulatory responses. Anti-TNF agents are a group of monoclonal antibodies engineered to inhibit the response to this cytokine for antiinflammatory purposes. The clinical experience of the use of these drugs in neurological conditions like multiple sclerosis showed controversial results. Evidence in favor of the employment of anti-TNF agents for the treatment of epilepsy are still limited to certain forms of disorders, notably Rasmussen encephalitis, and in carefully selected patients.

**Key words:** Adalimumab, TNF, Cytokine, Epilepsy, Neuroinflammation

## Background

Understanding the involvement of inflammatory responses in epileptogenesis has been the object of several studies in the last years (1, 2). Seizures can elicit inflammatory responses and, in turn, regional inflammation can contribute to the development and persistence of seizures (3). Neuroinflammatory responses are also primed in a group of disorders of the central nervous system (CNS) mediated by neural-specific autoantibodies and associated with seizures (4-6). Inflammation within the brain tissue is not always detrimental, since different neurotrophic and homeostatic mechanisms are also governed by inflammatory mediators (7). In this complex association, the role of cytokines has been of interest for therapeutic purposes and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), being involved in both inflammatory and neuromodulatory pathways, can represent a possible pharmacological target for many neurological pathologies (8-16). To understand

the therapeutic perspectives of anti-TNF- $\alpha$  agents, we review the biological functions of this cytokine and the effects of TNF inhibitors in patients with epileptic syndromes and other disorders of the CNS.

## Synthesis of TNF and molecular mechanisms of action

TNF- $\alpha$  is an effector cytokine of the TNF superfamily that regulates cell homeostasis and immune-inflammatory pathways (17). This pleiotropic cytokine is encoded by the *TNF* gene, located on chromosome 6 (6p21.33) and synthesized as a 26 kDa monomeric type 2 transmembrane precursor protein (tmTNF). The cytoplasmic terminal portion of the precursor is cleaved by a TNF- $\alpha$  converting enzyme (TACE; ADAM17), releasing a soluble 17 kDa cytokine (sTNF) (18). Both sTNF and tmTNF need to aggregate in homotrimers to exert their biological functions (19). Homotrim-

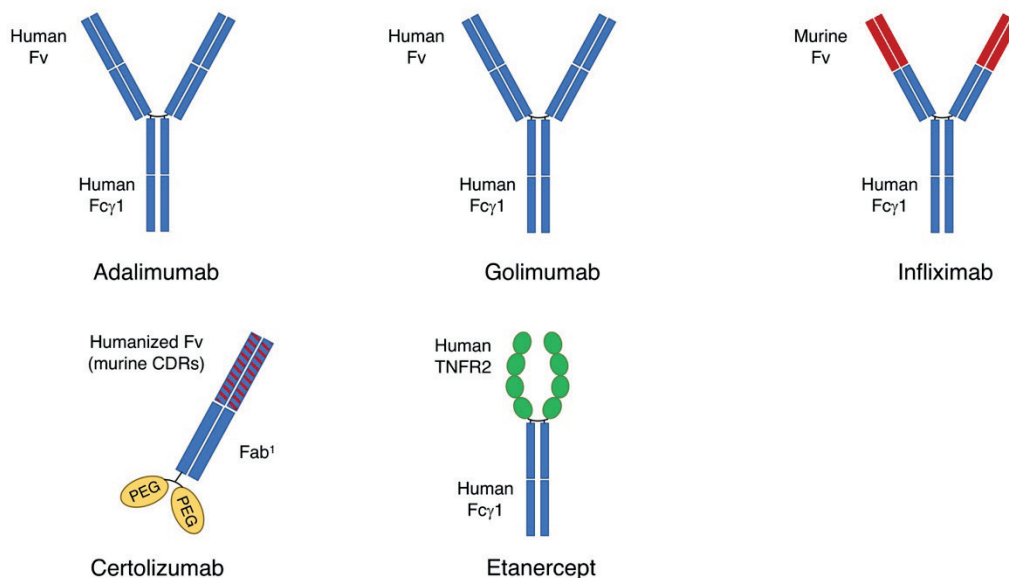
ers of sTNF or tmTNF can interact with two transmembrane glycoprotein receptors, TNF receptor 1 (TNFR1, also known as TNFRSF1a, p55TNFR, p60, CD120a) and TNF receptor 2 (TNFR2, also known as TNFRSF1b, p75TNFR, p80, CD120b), that are in turn preassembled as homotrimers (20). These receptors differ in the affinity for ligands, in their cellular expression profiles and in the downstream signaling involved (19). This latter is finely balanced and depends on the cell type and activation status, on TNF production and on the activity of TACE (21). TNFR1 is expressed by a wide range of cells and can be activated primarily by sTNF and to a lesser extent by tmTNF (22). TNFR2 is preferentially expressed on the surface of immune cells and endothelial cells and responds mainly to tmTNF (22). The responses to TNFR1 result in divergent outcomes, such as proliferation, apoptosis or production of cytokines, depending on the effectors involved, such as Nuclear Factor Kappa-B, C-Jun N-terminal Kinase, p38 and the acid sphingomyelinase-ceramide system (19, 22). Of note, the intracellular domain of TNFR1 can activate cell death pathways through a death signaling complex (19). The response to TNFR2 is more restricted and involves inflammatory and survival pathways, like the phosphatidylinositol 3-kinase-dependent pathway

that promotes neuron cells survival (23). It is possible for TNFR2 to perform a ligand passing towards TNFR1 (24). Additionally, two forms of reverse signaling have been described and involve respectively the cytoplasmic domain of TNFR2, via MAP kinase and p38 pathways, or the intracellular domain of tmTNF that is capable to activate pro-inflammatory responses once cleaved (25, 26).

### Anti-TNF agents and their employment in disorders of central nervous system

Since the assessment of the efficacy of an anti-TNF- $\alpha$  agent in patients with rheumatoid arthritis, different molecules with a TNF-inhibitory effect have been authorized for the treatment of polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and inflammatory bowel diseases (27). Figure 1 illustrates the anti-TNF agents currently approved for therapeutic use and their molecular structures (28). All these molecules consist in monoclonal antibodies (MAbs), that result from gene splicing and mutation techniques (29).

Infliximab, adalimumab and golimumab are full-length bivalent IgG1 MAbs with a capability to ac-



**Figure 1.** Molecular structure of the anti-Tumor Necrosis Factor (TNF)- $\alpha$  agents currently approved by the Food and Drug Administration. Human derived is indicated in blue, mouse-derived in red. CDR: Complementary Determining Regions; Fab: Fragment antigen-binding; Fc: Fragment crystallizable; Fv: Fragment variable; TNFR2: TNF receptor 2.

tivate complement and to bind Fc-receptor (28, 30). While adalimumab and golimumab are fully human antibodies, infliximab is a chimeric product constituted by mouse-derived amino acids (25%) and by human amino acids (75%) (28, 30). Certolizumab is a monovalent Fab<sup>1</sup> fragment of a humanized IgG1 antibody containing amino acid sequences derived from a mouse anti-TNF MAb and is PEGylated to enhance half-life and solubility and lacks effector functions due to the absence of a Fc region (28, 30, 31). Etanercept is constituted by the extracellular portions of human TNFR2 and the Fc portion of human IgG1. The MAbs can act both by blocking the cellular functions mediated by TNF-receptors (antagonistic effect), or through a reverse signaling via tmTNF, with an agonistic action (28). All TNF-inhibitors are administered in a parenteral way and display differences in mechanisms of action, pharmacokinetic profiles and thus in clinical efficacy (32).

The literature about the employment of TNF-inhibitors in neurological disorders is primarily focused on the treatment of multiple sclerosis (33, 34). However, two clinical trials raised the concern of a disease progression in some patients that were receiving TNF-inhibitors, based on clinical and radiological signs (33, 34). The occurrence of both inflammatory demyelinating and non-demyelinating events further emerged from different cases and case-series of patients treated for non-CNS related disorders (35-46). Although a causal correlation between demyelination and the use of anti-TNF- $\alpha$  has not been defined, some mechanisms may explain the adverse events observed (30, 47-49): (i) seen the inability of TNF-inhibitors to penetrate the BBB, they could not neutralize the TNF-driven inflammatory events (lack of entry theory) and this causes a relative increase of TNF concentration within the brain tissues as opposed to the periphery (sponge effect theory); (ii) the exposure to TNF-inhibitors was associated to an enhanced activity of peripheral autoreactive T cells, that could penetrate the BBB and sustain inflammatory and demyelinating events in the CNS; moreover, some patients may have *per se* an increased serum neutralization capacity of TNF- $\alpha$  and display an enhancement of this adverse effect; (iii) the use of anti-TNF- $\alpha$  agents may induce a downregulation of IL-10 and an upregulation of

IL-12 and IFN- $\gamma$ ; (iv) TNF-inhibitors may activate or reactivate a latent infection, which can trigger an immune-mediated demyelination; (v) the use of TNF-inhibitors may reduce the expression of TNFR2 receptors within the brain tissues, impairing the course of reparative processes. These theories, although specifically referring to demyelinating events, may suggest a detrimental role of TNF-inhibitors in the treatment of different neurological disorders.

### Mechanisms of epileptogenesis mediated by TNF- $\alpha$

TNF- $\alpha$  has been implicated in the pathogenesis of several neuropathological conditions including ischemia, and post-traumatic or excitotoxic brain injury (50-52). Albeit investigated by several studies, the involvement of TNF- $\alpha$  in epileptogenesis has not been completely clarified (2). Reportedly, the cytokine can influence neuronal cells by direct interaction or through the expression of neurotransmitter receptors on glial cells (53, 54) and it is also thought to create alterations in the permeability of the blood brain barrier (55, 56). More lines of evidence emerge from experiments in animal models that revealed a controversial role of TNF- $\alpha$  in epileptogenesis and highlighted three aspects that can determine its involvement: the cellular source of the cytokine, its concentration within brain tissues and the type of receptor predominantly expressed by the cells (1, 57, 58). Some authors evidenced how TNF- $\alpha$  displayed an inflammatory and degenerative effect when secreted by astrocytes, as opposed to a more tissue repair and remyelination-oriented outcome when released by microglial cells (59-61). Secondly, mice overexpressing TNF- $\alpha$  in high amounts by neurons and astrocytes were more prone to develop brain injury and neuronal deficits, while a milder overexpression in astrocytes was associated with a decrease in seizure susceptibility (61, 62). Finally, while signaling via TNFR1 elicits proinflammatory and proconvulsivant effects, responses to TNFR2 display a more anticonvulsivant and neurotrophic orientation (58).

This latter feature was well defined in murine models. Mice overexpressing TNF- $\alpha$  or knock out for TNFR1 showed reduced seizure duration, as op-

posed to those knock out for TNFR2 or for both the subtypes of receptor (62). Moreover, the intratissutal administration of human TNF- $\alpha$  (more specific for mouse TNFR1) did not affect seizure duration, as opposed to the administration of murine recombinant TNF that reduced the duration and the number of kainic acid-induced seizures (62). The responses activated by TNFR1 are still poorly characterized. Seemingly, the death signaling complex activated downstream this isoform of the receptor contributes to seizure-related brain injury and in experimental models of seizures neutralizing antibodies to TNF- $\alpha$  can reduce the entity of cell damage within brain tissues (63). These evidences were further confirmed by a study conducted on hippocampal tissues from patients with intractable temporal lobe epilepsy, where TNFR1 pathways resulted predominant and related to the activation of apoptosis pathways (and thus to the seizure-induced brain injury) (64). Other studies evidenced how TNFR1 may be involved in post-translational mechanisms that regulate expression and turnover of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), gamma aminobutyric acid (GABA) and N-methyl-d-aspartate (NMDA) receptors (53). Particularly, evidences suggest that glutamatergic transmission and glutamate synthesis are upregulated in response to TNF, while GABA-ergic transmission is attenuated via induction of endocytosis of GABA<sub>A</sub> receptors (53, 65). The disclosure of more details about the mechanisms activated by TNFR1 signaling may be of key importance for therapeutic reasons and should be investigated by further studies.

### Use of anti-TNF agents in epilepsy

The literature covering the use of anti-TNF agents for epileptic diseases is scanty. A prospective, open-label study by Lagarde and colleagues was conducted with the administration of adalimumab to 11 patients with Rasmussen Encephalitis (RE) refractory to other immunotherapies (e.g., corticosteroids, azathioprine, intravenous immunoglobulins) (66). The primary outcome was the decrease of seizures frequency, considering “responders” patients experiencing a decrease in seizure frequency by at least 50%. As secondary outcome, the

neurologic and cognitive outcomes and the side effects of the treatment were evaluated. Despite the fact that none of the patients became seizure free, five patients responded to the treatment and another one experienced a transitory decrease in the frequency of seizures. A stabilization of cognitive decline was observed in three of the five patients. Only one patient had to discontinue adalimumab, following an elevation of blood creatine kinase levels. The response to the treatment was more evident in patients with slowly progressive forms of RE and those individuals carrying autoimmune diseases, such as uveitis and juvenile arthritis. Seen the absence of a severe motor and cognitive deficiency, none of the responders underwent hemispherectomy, although this measure was necessary for three patients that faced a severe progression of the disease (66). Beside this study, Goyal and colleagues reported the case of a 12-year-old girl suffering from a granulomatous disease and RE (67). After several attempts to treat seizures with different immunotherapies, the patient underwent a treatment with etanercept and azathioprine with no clinical improvement. As etanercept was interrupted and relayed with infliximab, the young girl showed an 85% reduction in seizure frequency and duration and an improvement of speech and memory (67).

Overall, these results encourage further studies to assess whether adalimumab or other TNF-inhibitors could be effective for the treatment of some forms of RE, refractory to immunotherapies, but not matching the full criteria for a surgical approach. Patients, with slowly progressive forms may be good candidates for a treatment with anti-TNF- $\alpha$  agents (66). A possible disadvantage of immunotherapy in RE is that it can slow down the progression of the disease and preserve the functional outcome, but with little effect on seizures, hence leaving patients in a steady state without the possibility to undergo hemispherectomy (68). Additionally, the dual nature of the responses to TNF- $\alpha$  in epileptogenesis must be kept in mind in order to avoid an unfavorable outcome with an increase in seizures frequency and in the entity of brain injury. Future therapeutic agents may discern TNFR1 and TNFR2 signaling, in order to silence the proinflammatory and proepileptic responses to the former and sustain the mechanisms of tissue preservation and repair activated by the latter (51).

## Conclusions

Targeting TNF- $\alpha$  for the treatment of disorders of the central nervous system appears to be premature considering the controversial effects reported. A more univocal response may result from a better understanding of the effects of TNF inhibition on the balance between TNFR1 and TNFR2 signaling. This aspect is particularly important for epilepsy syndromes, where the aim should be to downregulate the responses to TNFR1 and upregulate certain pathways activated by TNFR2. The favorable outcome of some patients with RE following the administration of adalimumab can be promising but is referred to a limited number of subjects affected by a disease with a preponderant inflammatory etiology. Further studies including other forms of epileptic diseases may be determinant for understanding whether anti-TNF- $\alpha$  agents can be effective as therapeutic agents.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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