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The contribution of tumor necrosis factor to multiple sclerosis: a possible role in progression independent of relapse?

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Abstract

Tumor necrosis factor (TNF) is a pleiotropic cytokine regulating many physiological and pathological immune-mediated processes. Specifically, it has been recognized as an essential pro-inflammatory cytokine implicated in multiple sclerosis (MS) pathogenesis and progression. MS is a chronic immune-mediated disease of the central nervous system, characterized by multifocal acute and chronic inflammatory demyelination in white and grey matter, along with neuroaxonal loss. A recent concept in the field of MS research is disability resulting from *Progression Independent of Relapse Activity (PIRA)*. PIRA recognizes that disability accumulation since the early phase of the disease can occur independently of relapse activity overcoming the traditional dualistic view of MS as either a relapsing-inflammatory or a progressive-neurodegenerative disease. Several studies have demonstrated an upregulation in TNF expression in both acute and chronic active MS brain lesions. Additionally, elevated TNF levels have been observed in the serum and cerebrospinal fluid of MS patients. TNF appears to play a significant role in maintaining chronic intrathecal inflammation, promoting axonal damage neurodegeneration, and consequently contributing to disease progression and disability accumulation. In summary, this review highlights the current understanding of TNF and its receptors in MS progression, specifically focusing on the relatively unexplored PIRA condition. Further research in this area holds promise for potential therapeutic interventions targeting TNF to mitigate disability in MS patients.

Keywords TNF biology, MS pathology, PIRA, MS lesions, Chronic compartmentalized inflammation, Neurodegeneration, Biomarkers, Disease progression

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated and neurodegenerative disease of the central nervous system (CNS) affecting millions of people worldwide [1] and it is the most common cause of non-traumatic neurological disability in young adults [2].

MS is a complex multifactorial disease caused by complex gene–environment interactions and characterized by multiple pathological hallmarks, ranging from immune dysregulation and neuroinflammation to neurodegenerative mechanisms [3].

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Several molecular changes, including increases in cytokines, chemokines, nitric oxide, reactive oxygen species, glutamate, and free radicals, affect the pathogenesis and the course of MS [4].

The clinical course of MS is highly variable, heterogeneous, and unpredictable at the individual level. Generally, it is characterized by transient and recurrent episodes of focal acute CNS inflammation early on, with complete or partial resolution (relapsing–remitting MS–RRMS) and, over time, by a prominent process of neurodegeneration, resulting in a late, slow, steady, progressive accumulation of physical disability and cognitive impairment (secondary progressive MS–SPMS) [5]. On the other hand, a gradual and continuous neurological decline from the disease's onset characterizes the MS subtype known as primary progressive MS (PPMS) [5–7].

Beyond this traditional phenotypic categorization, it is now clear that MS progresses along a continuum from RRMS to progressive MS (PrMS), with distinct levels of neurologic reserve explaining phenotypic differences [8].

This emerging view of MS as a single-stage disorder in which all patients exhibit a progressive course since disease onset, which can overlap with relapses [6, 8], is supported by the new concept of progression independent of relapse activity (PIRA) [9]. The term PIRA, proposed by Kappos et al., refers to the progressive clinical deterioration occurring in many RRMS patients without signs of inflammatory activity [9]. This notion aligns with several previous observational studies showing that disability accumulation is largely independent of superimposed focal inflammation, referring to additional inflammatory lesions, and is undetectable by conventional clinical-radiological parameters [10–13].

Although the frequency of PIRA has been reported within the first 5 years following the first MS-related clinical attack, its identification in clinical practice remains unclear due to the lack of standardized definitions (such as a time window after the last relapse) and/or measures to detect it (such as based on the expanded disability status scale—EDSS—score or an increase in composite measures) [14].

The mechanisms driving PIRA have yet to be fully elucidated but are undoubtedly associated with smouldering inflammatory and neurodegenerative processes. In a prospective, large sample size study, Cagol et al. showed that RRMS patients with PIRA (defined as a 6-month confirmed disability progression with no relapse during the 90 days before and the 180 days after the initial increase in the *EDSS* score) exhibit more pronounced diffuse cerebral cortical volume loss [15]. This finding aligns with several studies demonstrating that grey matter (GM) atrophy is predictive of long-term physical and cognitive disability [16] and conversion to PrMS [17].

Cerebral GM damage, which manifests as both focal cortical lesion(s) and diffuse cortical and deep GM atrophy, provides one of the best clinical correlations with irreversible disability accumulation [16, 18] and it is topographically associated with aberrant tertiary B-cell-enriched lymphoid structures affecting the cerebral meninges [19]. The extent of meningeal immune infiltration is correlated with the degree of subpial GM demyelination, microglial activation, and axonal loss [19–22].

MS patients with a progressive and severe course of the disease also display chronic active lesions (CALs), a subset of white matter (WM) lesions characterized by an inactive core surrounded by a "rim" of activated microglia [23–25]. CALs are associated with nearby persistent demyelination and axonal loss, even in the absence of blood–brain barrier (BBB) damage [23–25].

Molecular-neuropathological studies on progressive MS patients supported the hypothesis that soluble factors (chemokines and cytokines) produced by meningeal tertiary lymphoid structures and/or circulating immune cells may diffuse throughout the cerebrospinal fluid (CSF) into the cortex, inducing brain damage either directly or indirectly through microglial activation [26]. In this regard, Kosa and colleagues found that CSF biomarkers associated with immune-related pathways correlate with clinical and imaging MS severity outcomes and predict future disability [27].

All these findings suggest that chronic inflammation in the CNS continuously disturbs neuroaxonal homeostasis, leading to prominent neurodegeneration, even outside of MS relapses, especially at the progressive stage [28]. This confirmed that compartmentalized inflammation (involving the CSF, meninges, and parenchyma) is a major mechanism driving progressive multiple sclerosis.

Among the different cytokines found to increase in the CSF of MS patients [26], tumor necrosis factor (TNF) represents one of the main proinflammatory cytokines correlated with the degree of disability in patients with progressive MS [29].

Selmaj et al. also provided significant evidence that an increase in TNF occurred locally within the CNS of MS patients, specifically in acute and chronic active MS brain lesions [30]. This further suggests that the combination of inflammation, demyelination and neurodegeneration is a highly specific process in MS, as supported in a study by Fischer et al. [31].

TNF exerts its potent proinflammatory activity by activating two specific TNF receptors (TNFRs): TNF receptor type-1 (TNFR1) and type-2 (TNFR2) signaling [32, 33]. In addition to this inflammatory action, TNF has excitotoxic [34] and necro-apoptotic effects on oligodendrocytes [35, 36] and neurons mainly through TNFR1 activation [37].

A post-mortem study revealed that an imbalance of TNF receptor type-1 (TNFR1) and type-2 (TNFR2) signaling plays a role in determining the severity of MS [38], demonstrating a strong correlation between compartmentalized inflammation and the high expression of genes involved in the TNFR1 signaling cascade [38].

This comprehensive review explores the potential impact of TNF pathway alterations on MS progression and the potential of selective targeting and detection of TNF-TNFRs, specifically focused on the PIRA condition, on which many questions persist regarding its frequency, pathological determinants, treatment, and implications [39]. Therefore, understanding the role of TNF signaling in PIRA could shed light on the neurodegenerative mechanisms that drive the progression of RRMS from the earliest stages of the disease [39].

TNF biology, cellular production and signaling pathways

The master proinflammatory cytokine TNF has been shown to have a broad spectrum of cellular effects, including inflammatory response, cellular activation, and programmed cell death [40]. TNF belongs to the TNF superfamily, which includes 19 ligands produced primarily by monocytes/macrophages but also by T and B lymphocytes, smooth muscle cells, adipocytes, osteoclasts, and fibroblasts, although in smaller quantities [40, 41].

TNF is expressed initially as a transmembrane protein (mTNF, 26 kDa 233-amino-acid), which requires proteolytic cleavage by the TNF converting enzyme (TACE) to release soluble TNF (sTNF, 17 kDa 157-amino-acid). mTNF and sTNF are produced by a wide range of peripheral and central immune cells, such as activated macrophages, effector CD4 + and CD8 + T cells, B lymphocytes and microglia, as well as neurons, oligodendrocytes, and astrocytes [42].

Both mTNF and sTNF are biologically active and exert their effects by modulating a complex signaling pathway with wide-ranging downstream responses through two distinct surface receptors belonging to the TNFRs-superfamily (comprising 29 receptors): the TNF receptor-superfamily member 1A (TNFRSF1A-TNFR1; p55/60; CD120a) and TNF receptor-superfamily member 1B (TNFRSF1B-TNFR2; p75/80; CD120b) [40–42].

The two receptors differ significantly in structure, binding affinity, localization, function and activation of signaling pathways [43, 44].

TNFR1, which is expressed on the membrane of all cell types except for erythrocytes, shows a high affinity for sTNF, promoting both necrosis and apoptotic pathways as well as proinflammatory signaling [45] through its death domain (DD), which, when activated by TNF binding, recruits the TNFR1-associated death domain (TRADD). TRADD can in turn recruit Fas-associated death domain (FADD) and receptor-interacting serine/threonine-protein kinase 1 (RIPK1), which can either lead to necroptosis through RIPK3 and mixed lineage kinase domain-like pseudokinase (MLKL) activation or apoptosis through caspase 8 and caspase 3 recruitment [46, 47]. In contrast, proinflammatory signaling is mediated by TNFR-associated factor 2 (TRAF2) activation of mitogen-activated protein kinases (MAPKs), such as c-Jun-N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and the transcription factor nuclear factor-κB (NFκB) [46].

TNFR2, which is expressed only in a few cell types (neurons, oligodendrocytes, microglia, and T lymphocytes), mediates local homeostatic effects, such as cell survival, tissue regeneration and inflammation, by preferentially binding to mTNF [48, 49]. Unlike TNFR1, TNFR2 does not have a death domain. Nevertheless, a recent study has shown that under some circumstances, TNFR2 signaling also has pro-apoptotic effects by amplifying TNFR1-mediated stimulation of apoptosis or cooperating in the binding of TNF to TNFR1 [42, 50]. However, the mechanism of TNFR2-mediated cell death is still unclear, and homeostasis and cell survival remain the primary functions exerted by TNFR2-mediated signaling through TRAF (1/2) activation of MAPKs (JNK and ERK), protein kinase B (Akt), and NFκB [46].

Therefore, albeit in different ways, both TNFR1 and TNFR2 signaling may lead to NF-κB and MAPK activation, increasing the expression of inflammatory genes encoding chemokines and cytokines (including TNF itself) [43, 44] and inducing antiapoptotic transcriptional programs that promote cell survival, cell proliferation and cell differentiation [51, 52].

This duality of TNFR signaling, which can induce cell survival and cell death, depends on the cellular environment, the relative surface levels of TNFR1 and TNFR2, and their cellular activation status (Fig. 1). However, the effects of altering the TNFR1/TNFR2 balance under normal and altered physiological conditions remain unclear [53].

Potential pathological implications of TNF-TNFRs impairment in MS and EAE

Several studies on human and experimental MS have demonstrated the involvement of TNF in various pathological hallmarks of MS, including neuroinflammation, neurodegeneration and demyelination.

The role of TNF in neuroinflammation associated with MS

TNF plays a crucial role in several immune-mediated conditions, including rheumatoid arthritis [54], systemic lupus erythematosus [55] and Crohn's disease

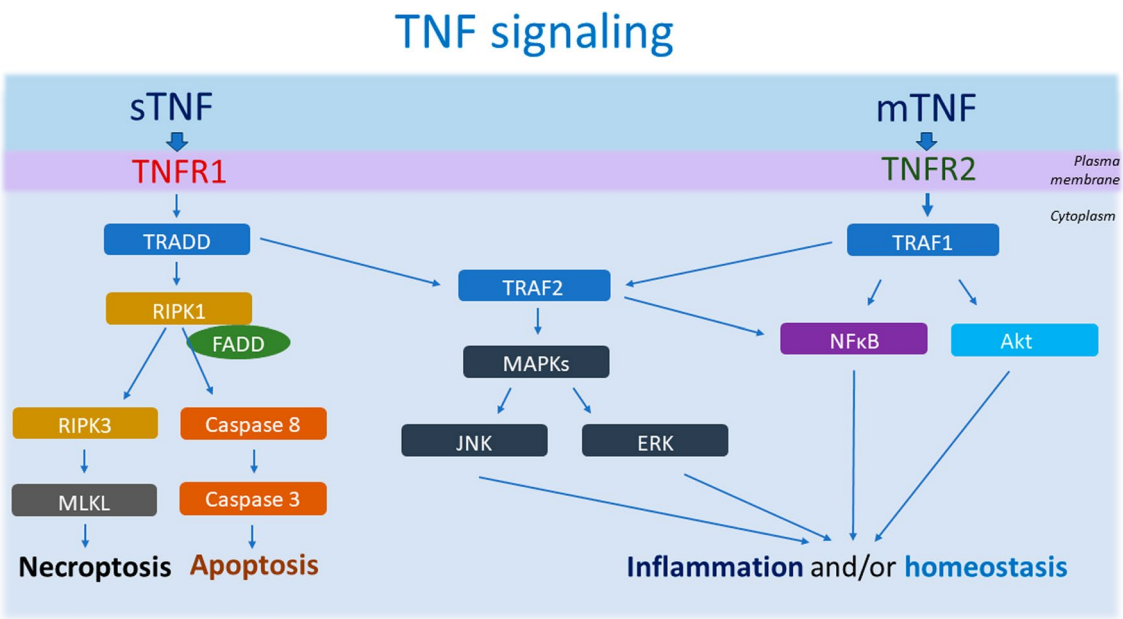

Fig. 1 TNF signaling. TNF signaling is mediated by two isoforms (mTNF and sTNF), which exert their effects by modulating a complex signaling pathway through two distinct surface TNF receptors: TNFR1 and TNFR2. TNFR1 shows a high affinity for sTNF, which once bound, recruits TRADD. TRADD binds to FADD and RIPK1, leading to necroptosis through RIPK3 and MLKL activation, or apoptosis through caspase 8 and caspase 3 activation. On the other hand, mTNF interacts with TNFR2, inducing inflammation and homeostasis through TRAF1/2 activation of JNK, ERK MAPKs, Akt and/ or NFκB

[56]. As a potent mediator of inflammation, principally via TNFR1 signaling, TNF is considered one of the major cytokines involved in the pathogenesis of MS [32, 33].

A relevant action of TNF is to activate T lymphocytes, enhancing their proliferation and recruitment and increasing proinflammatory cytokine production in the CNS by inducing the activation of NF-κB signaling pathways [57]. TNF-dependent T-cell activation contributes to blood–brain barrier (BBB) damage via secondary meningeal mast cell activation and therefore promotes further inflammatory cell influx with consequent myelin and neuronal damage [58, 59].

Not surprisingly, elevated TNF production is found in MS patients [30, 60] and in experimental autoimmune encephalomyelitis (EAE), the most commonly used murine model of MS [60].

High TNF levels are found in active demyelinating lesions [29] and in the serum and CSF of MS patients [61–63], in correlation with the increase in the degree of disease severity [63–66]. In EAE mice, TNF mRNA expression is upregulated in the CNS in parallel with disease progression, and its exogenous administration increases EAE severity [60, 67] since it is involved in immune cell (macrophage and T cell) activation and infiltration into the CNS [66].

The use of EAE transgenic mice for TNF and TNFRs has significantly contributed to understanding the pathological role of TNF in MS [49].

Compared with wild-type (WT) EAE mice, TNF-gene knockout (KO) EAE mice exhibit a milder disease course due to reduced leukocyte intrathecal trafficking and BBB permeability [68]. This evidence suggests that TNF signaling alterations are involved in the (early) pathological MS mechanisms that occur in the CNS [68].

In addition to cytokines, several studies have investigated the role of TNFRs in MS pathology. Specifically, compared with WT EAE mice, TNFR1 KO EAE mice showed a reduction in immunopathological signs and symptoms of the disease, whereas TNFR2 KO EAE mice showed more severe disease symptoms, enhanced T-cell infiltration in the CNS and diffuse demyelination [69].

Intriguingly, TNFR2 has recently been demonstrated to be crucial in regulating T-cell biology [69]. Specifically, it is known to be expressed by *regulatory T cells* (T_{regs}) and is involved in their proliferation and expansion [70]. T_{regs} are a specialized subpopulation of T cells that act to suppress immune response, inhibiting T cell proliferation and cytokine production [71], T_{regs} are essential for maintaining immune homeostasis and preventing autoimmunity [67–74]. Not surprisingly, impaired functional suppression of T_{regs} in response to autoreactive T

cells is typically reported in MS [75]. In line with this, a recent study on T_{reg}-restricted TNFR2-deficient mice with induced EAE revealed that these mice developed an aggressive disease, indicating the critical protective role of TNFR2 signaling [76]. However, the significance of intrinsic TNFR2 signaling in T_{reg} cells in vivo remains incompletely defined [76].

These findings support the critical role of TNFR1 signaling in the induction of a proinflammatory environment in the CNS [68]. In contrast, TNFR2 appears to be involved in neuroprotection and repair processes [68].

The role of TNF in neurodegeneration, demyelination and remyelination associated with MS

In addition to immune cell activation and infiltration, TNF signaling engages in neurodegenerative processes. TNF promotes neuronal excitotoxicity and oligodendrocyte death, acting directly on neurons and glial cells through TNFRs, with further TNF release [46, 77].

An elegant study by Centonze et al. showed that increased concentrations of TNF released by activated microglia induce changes in the expression and physiological properties of glutamate AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors (AMPRs) and NMDA (*N*-methyl-*D*-aspartate) receptors (NMDARs) in EAE mice [78]. Specifically, TNF acting on neuronal TNFR1 receptors causes excitotoxicity by increasing the surface expression of AMPARs and the activation of NMDARs, prolonging the duration of the glutamate postsynaptic response [78].

In addition to excitotoxicity, TNF-TNFR1 signaling is involved in triggering oligodendrocyte apoptosis [35]. Consistent with this, TNF-overexpressing transgenic mice developed spontaneous demyelinating lesions like those observed in MS [35, 79, 80]. On the contrary, TNF through TNFR2, facilitates remyelination by promoting oligodendrocyte differentiation in EAE [81]. Furthermore, TNFR2-KO mice develop more severe EAE motor disease than WT mice [81–83]. In TNFR2 conditional KO EAE mice, a novel transgenic mouse with selective TNFR2 ablation in oligodendrocytes, altered TNFR2 signaling results in impaired remyelination [83].

These findings suggest that TNF could exhibit a bimodal effect, depending on the receptor it binds to, thereby triggering distinct signaling pathways. In MS, the TNFR1 signaling cascade plays a harmful role, whereas TNF acting via TNFR2 exerts a protective effect, attenuating the disease's aggressive course. Enhancing TNFR1 and weakening TNFR2 signaling, the TNF contributes to MS pathogenesis and progression, leading to inflammatory demyelination, remyelination failure, and neuronal functional damage, including synaptic impairment.

Increased intrathecal TNF expression and impaired TNF-TNFRs signaling in association with meningeal inflammation in MS

Increased levels of proinflammatory cytokines and cytotoxic mediators are found in the CSF of MS patients [26]; specifically, CSF levels of TNF are correlated with the degree of disability in patients with PrMS [26, 29, 84, 85] but are not detected in patients with other neurodegenerative diseases [30]. This increase is determined by immune cell infiltration into the CNS; in particular, lymphocytes and macrophages enter the brain through the perivascular space and meninges, where they can release cytokines and chemokines that trigger glial cells and neurons to produce additional inflammatory mediators, such as IL-1β, TNF, and IFN-ɣ [86]. Mounting intrathecal neuroinflammation induces a local and chronic immune response that alters synaptic transmission and neuroaxonal homeostasis [20], leading to an increasingly inflammatory environment in the CSF, which bathes the cortical layers [26, 84]. In this regard, a strong correlation was found between CSF/meningeal inflammation and the degree of cortical damage, microglial activation, and axonal loss [20, 26, 84]. Chronic inflammation causes GM damage in MS from the earliest stages of the disease. This leads to disability accumulation independent of acute inflammation due to the decreased capacity of the compensatory mechanisms, including neuroplasticity, remyelination, redistribution of sodium channels along axons to maintain nerve conduction and expression of neurotrophic factors to support neuron survival and repair, as well as immune modulation [20, 28, 87–89]. Early cortical GM damage is indeed related to a more severe and rapid disease course in terms of disability progression and cognitive impairment [28].

In this regard, it has been demonstrated that neuroinflammation increases with MS progression, identifying specific inflammatory pathways correlated with MS progression, which include both the innate and adaptive immune pathways of T helper (Th) 17 (IL17, GM-CSF and IL6), Th1 (IFNγ and TNF) and Th2 (IL13 and IL4) phenotypes [27]. Moreover, Magliozzi et al. showed that meningeal inflammation specifically alters the balance between TNFR1 pro-cell death and TNFR2 pro-cell survival signaling, causing more severe disease manifestations from the early stages [38]. In addition, this study not only confirmed elevated TNF levels in the CSF of MS patients at the time of diagnosis but also revealed greater TNFR1 gene overexpression in MS patients, especially in the cortical GM tissues of progressive disease patients [38]. These results are in line with a recent study by Picon and colleagues that provides substantial evidence for TNF-mediated activation of necroptotic signaling via TNFR1 in cortical neurons of progressive MS patients

[37]. In fact, the study demonstrated increased expression of multiple steps in the TNF-TNFR1 signaling pathway leading to necroptosis, including the key proteins TNFR1, FADD, RIPK1, RIPK3 and MLKL [36].

All these results support the hypothesis that neurodegeneration in MS is mainly driven by chronic inflammation in the CNS, with a preponderant involvement of activated TNF–TNFR1 signaling.

Evidence for TNF involvement in MS lesion formation

Degenerative processes include demyelination, axonal injury, and neuron loss, and result in multifocal WM lesions and diffuse GM damage in subpial and subventricular regions close to the CSF and meninges [90]. Significant upregulation of TNF and TNFR1 was found in white matter (WM) and subpial GM lesions [81].

WM lesions can be classified as active, chronic active (CALs; smouldering, slowly expanding, mixed active/inactive), remyelinating, or chronic inactive lesions [92]. Active lesions develop from normal-appearing white matter (NAWM) and are characterized by areas of demyelination and activated macrophages and microglia. These lesions can remyelinate in the presence of activated microglia or evolve into CALs or inactive lesions [93]. CALs exhibit a demyelinated hypocellular nucleus and rims of iron-laden activated microglia [94, 95], while inactive lesions are well-defined areas of demyelination and axonal degeneration in the absence of inflammation [23, 80, 93].

Chronic compartmentalized inflammation leads to the formation of CALs, which increase in number as the disease progresses [31, 96, 97]. In fact, they represent more than half of all focal WM lesions, especially in progressive MS patients [98], depicting a relevant pathological finding associated with a severe disease course mediated by neuroaxonal damage in the absence of superimposed acute inflammatory activity [23, 94, 97].

The presence of TNF in CALs and its absence in inactive lesions is a noteworthy finding consistent with previous observations indicating immunoreactivity primarily in activated microglia and T cells at the lesion edge [30, 95]. In addition, a seminal study by Jackle et al. explored the immunological-molecular profile of CALs; through microarray analysis, they found an upregulation of different genes associated with immune functions, including those for TNF and its receptors, indicating its significant role in the formation of CALs [99]. Specifically, the transcript expression of the TNFR1 gene increased almost fivefold in these lesion types [99]. These results suggest an ongoing inflammatory response associated with the TNF and TNFR1 overexpression in CALs, which contributes to the exacerbation of MS outcomes.

Furthermore, TNF and TNFR1 levels also increase in cortical lesions [38]. GM damage, including cortical lesions and atrophy, is already present in the early phase of MS [28, 80, 100, 101] and becomes more prominent during the disease progression [102]. Early cortical involvement is related to a more severe and rapid disease course in terms of disability progression and cognitive impairment. The transcriptional profile of chronic subpial GM lesions isolated from MS brain samples with prominent meningeal inflammation, revealed an upregulation of TNFR1 and genes encoding caspase 1, proinflammatory cytokines and chemokines, consistently with skewing toward a detrimental environment and proinflammatory microglia phenotype within these lesions [91]. This evidence is also supported by the study of Magliozzi et al., which demonstrated that in subpial GM lesions of progressive MS patients, TNFR1, and not TNFR2, was exclusively increased [38]. Overall, these studies highlight TNF-TNFR1 signaling as a potential future therapeutic target for mitigating the impact of both CALs and GM lesions in MS.

Exploring the potential role of TNF signaling in the emergence of PIRA

According to the newly proposed categorization, the different clinical MS phenotypes (RRMS, SPMS, PPMS, and PRMS) identified in 1996 [103] are summarized in relapsing–remitting disease versus progressive disease [104]. Both clinical forms of MS appear to reflect the same underlying disease process characterized by neuroinflammation and subsequent neurodegeneration [105, 106] present in all MS lesions across the entire disease course [105–110]. In this context, compartmentalized neuroinflammation appears crucial for the onset and progression of neurodegenerative mechanisms that result in axonal loss and brain atrophy [111], which are strongly correlated with long-term functional and cognitive disability [112].

Several studies have also proven the association between focal inflammatory activity and diffuse and regional atrophic changes [15, 113, 114]. Specifically, MS lesions cause brain volume loss through direct inflammatory damage leading to myelin and axonal loss and, indirectly, tissue loss following Wallerian degeneration [15].

In addition, evidence from neuropathological, imaging, and biomarkers studies suggests more continuous axonal loss across all clinically defined stages of MS, both in early and relapsing MS rather than in more advanced and progressive stages [9].

The classic RRMS/PrMS subdivision has been overcome since the emergence of a new concept of MS, evidence of progression independent of relapse activity (PIRA) [15].

PIRA represents the first and main event responsible for irreversible disability accumulation in adult patients with RRMS, which occurs in 80% to 90% of patients [9]. PIRA is already present in the early phases of disease and may even occur during disease-modifying treatments (DMTs) [15, 111, 112, 115]. Two similar important studies investigating PIRA in early MS patients showed that approximately one-fourth of patients with RRMS may develop PIRA during the first ten years of the disease [14, 116]. Patients who developed their first PIRA event very early in the disease course had an unfavourable prognosis [14].

PIRA occurs in approximately 5% of all patients with RRMS annually, causing at least 50% of all disability accrual events in typical RRMS [117]. In this regard, a recent study confirmed that up to 50% of disability accumulation in adult patients with RRMS is not associated with evident relapses [118]. Relapses may mask disease progression, and the gradual loss of function might go unnoticed by some patients and their physicians; this would explain why PIRA is underestimated in patients with RRMS [118].

Furthermore, patients with PIRA show significantly increased GM atrophy and a greater number of CALs, providing additional important evidence of the association between PIRA and diffuse neurodegeneration [15].

In PIRA, neuroinflammation is associated with several pathological processes, such as brain atrophy, failure of compensatory mechanisms and impaired remyelination [119, 120]. Understanding molecular mechanisms underlying TNF signaling and associated neuroinflammation in PIRA is crucial for developing targeted therapies to slow the MS progression and potentially identifying prognostic and predictive disease values associated with TNF-TNFRs levels.

Currently, there are no specific biomarkers for identifying PIRA conditions. Overall, the only biomarker of ongoing neuronal damage considered is serum neurofilament light chain (sNfLs). However, its association with long-term clinical outcomes or its ability to reflect slow and diffuse neurodegenerative damage in MS is not completely clear [121]. This lack of clarity is probably due to unstable measurements subject to physiological changes such as age or body mass index fluctuations [121, 122].

Although early treatment with DMTs delays the diagnosis of progression over time [123], the ability to target PIRA remains an unmet need, even during highly effective treatments [9, 117]. Nevertheless, several recent observational studies failed to confirm a beneficial association of DMT with PIRA [117, 124, 125].

Hence, identifying a biological target that specifically reflects current and future prognostic disability and irreversible CNS tissue damage due to PIRA is urgently needed.

Anti-TNF therapy and its potential use for PIRA

Based on the strong proinflammatory activity of the TNF, several anti-inflammatory drugs targeting TNF signaling have been developed and approved for treating inflammatory diseases, such as Crohn's disease, ankylosing spondylitis, and rheumatoid arthritis. Specifically, five TNF blockers are available for clinical use: infliximab, adalimumab, golimumab, certolizumab and etanercept. Anti-TNF serum is composed of either anti-TNF antibodies (infliximab, adalimumab, golimumab and certolizumab) or TNFR fusion proteins (etanercept) that act as antagonists by blocking TNF (both mTNF and sTNF) interactions with TNFRs [126]. Despite being considered relatively safe and effective for the above-mentioned diseases, severe effects associated with immune suppression have been reported in MS [66, 127]. In particular, a clinical trial of infliximab showed unfavourable results, with increased disease activity and MRI lesion load, proving the association of TNF inhibitors with CNS demyelination [127, 128]. Although the relationship between TNF blockers and demyelination remains uncertain, it is likely that these blockers are not selective, i.e., they block the interaction between TNFR1, which has a primarily proinflammatory effect, and TNFR2, which has a primarily protective effect. This finding confirms the crucial and controversial role of TNF in the CNS, which exerts both potent proinflammatory effects (via TNFR1) and essential protective functions (via TNFR2) under pathological conditions [31, 66]. Specifically, TNF through TNFR2 signaling modulates the reactivity of self-reactive T cells to self-antigens, promoting the expansion of Treg cells and, subsequently, the preservation of myelin oligodendrocytes [90]. Selective inhibition of TNFR1 and selective activation of TNFR2 through the use and even discovery of new antagonist and agonist antibodies could represent a new molecular target for developing therapeutic agents for MS [49]. A recent preclinical study showed that atrosab, a human monovalent antibody selectively against TNFR1 developed for treating inflammatory diseases, reduces disease severity. This preclinical evidence seems promising for finding novel effective drugs for MS and perhaps PIRA in the future [32].

The impact of DMTs on TNF-TNFRs serum levels in patients with PrMS

Peripheral TNF levels are elevated in PPMS patients and correlate with disease progression, while results for RRMS patients are inconclusive [49, 129]. The detection of soluble TNFRs (sTNFR1 and sTNFR2) in serum

has been suggested as a potential prognostic marker for PrMS [129, 130].

Consequently, researchers have focused on serum-detectable TNF-signaling to attempt to distinguish MS forms, monitor disease activity and assess treatment responses [49, 129, 130].

Several studies have shown that commonly used MS drugs can indirectly modulate TNF and sTNFRs expression [131–137]. Novel and increasingly effective DMTs approved in the last decades significantly impact the immune system, including TNF expression [131, 132]. These DMTs, including oral fumarates, glatiramer acetate (GA), teriflunomide and selective sphingosine 1-phosphate receptor (S1PR) modulators (Fingolimod and Siponimod), as well as cell-depleting therapies such as cladribine, anti-CD20 (Ocrelizumab) and anti-CD52 monoclonals (Alemtuzumab), reduce disease activity and disability progression, albeit in a different way [132]. GA treatment promotes Th2 and Treg expansion, releasing neurotrophic factors and anti-inflammatory cytokines, and, conversely, reducing pro-inflammatory mediators like TNF and TNFRs [133]. Teriflunomide, a chemotherapeutic agent, inhibits the proliferation of B cells, T cells, and macrophages by inserting itself into DNA strands, and selectively suppresses pro-inflammatory cytokines expression, such as TNF [134]. S1PR modulators sequester autoreactive lymphocytes within lymph nodes, preventing their infiltration into the CNS [135]. They also inhibit T cell differentiation into pro-inflammatory Th1 and Th17 cells, producing TNF [135]. Specifically, Fingolimod-treated mature dendritic cells (DCs) show impaired phagocytic capacity and down-regulated several pro-inflammatory cytokines, including TNF [136]. Lastly, a recent study by Nowak-Kiczmer et al. found that serum levels of sTNF-R1 and sTNF-R2 significantly differed between PPMS patients treated with Ocrelizumab and treatment-naïve progressive patients, with higher sTNF-R2 levels in the treated group [137].

By modulating TNF expression, DMTs help reduce inflammation and potentially slow down disease progression. This modulation can have significant consequences for PIRA, as it may help mitigate some of the pathological processes associated with the condition, such as brain atrophy, failure of compensatory mechanisms, and impaired remyelination.

Discussion

TNF plays a pivotal role in the pathogenesis of MS [32, 33]. Its pleiotropic effects are mediated through the interaction with two receptors: TNFR1 signaling appears to be involved in the induction of neuroinflammatory processes, while TNFR2 engages in cell survival neuroprotection and sustains homeostasis processes. The balance between TNFR1 and TNFR2 levels and their activation status determine the complexity of TNF-TNFRs pathways. Alterations in the TNFR1-TNFR2 balance have been confirmed in MS [53] in association with a more severe and early disease progression [38]. Transgenic EAE mouse models have contributed significantly to understanding the pathological role of TNF and TNFRs in MS [49]. TNF/TNFR1 KO mice exhibited a milder disease course [68, 69], whereas TNFR2 KO mice showed more severe EAE symptoms and diffuse demyelination [69]. Specifically, the selective ablation of TNFR2 in oligodendrocytes results in impaired remyelination [83]. Likewise, TNFR1 signaling activation by TNF mediates necroptosis and apoptosis in oligodendrocytes [35, 36] and causes neuronal excitotoxicity [78] and necroptosis in cortical neurons [81]. These processes contribute to inflammatory demyelinating processes and neurodegeneration. Therefore, it is unsurprising that TNF and TNFR1 are overexpressed in CALs and GM lesions in MS patients [30, 38, 95, 99], especially in those with progressive MS [38]. In addition, increased levels of TNF were detected in the CSF of MS patients [26]. High CSF TNF levels are associated with chronic compartmentalized inflammation, causing GM damage from the early disease stages, correlating with the degree of disability in patients with progressive MS [20, 26, 28, 29, 84, 85]. All these results (summarized in Table 1) suggest a possible role for TNF-TNFR1 signaling activation in disease progression independent of acute inflammation and in the decrease of compensation mechanisms following a neuronal insult [20, 28, 87, 88].

Neurodegenerative processes drive progression independent of relapse activity, PIRA, which is currently considered the main contributor to irreversible disability accumulation since the relapse-onset of the disease and throughout the entire disease course [9, 14, 15, 116, 117]. PIRA plays a significant role in worsening and transitioning to progressive MS. However, the definition of PIRA is not widely clarified as disease progression can be extremely gradual and slow compared to relapses. This makes PIRA underestimated and not so easily recognized [118]. Furthermore, consistent data have shown no beneficial effects of DMT on PIRA [117, 124, 125].

Similarly, TNF-TNFRs blockers used for the treatment of several inflammatory diseases are not only ineffective but also potentially harmful for MS patients [66, 128]. Their unselective action fails to preserve neuroprotective and cell survival processes associated with TNFR2 signaling.

For these reasons, understanding PIRA is crucial for developing effective MS therapies. Selective modulators targeting TNFRs (e.g., TNFR2 activation or TNFR1 silencing) could be promising therapeutic options.

Table 1 Studies on the role of TNF in MS and EAE

		Type Cells Involved	Effects	Effects	Relevance	Relevance in MS	References
MS patients	TNF in the MS CSF	Macrophages, T cells	Infiltration of activated macrophages/T cells in the brain parenchyma	MS lesions formation	Inflammation	Disability accumulation	[57–59]
		Neurons, Glial cells	Activation of neurons and glial cells	MS lesions formation	Neuroinflammation		[26, 29, 84, 85]
	TNF in MS Lesions	Neurons	Cortical lesions and Atrophy	GM demage	Neurodegeneration	Disability progression	[38]
		Microglia, T cells	Chronic active lesions	WM lesions	Demyelination		[99]
EAE model	EAE mice	Macrophages, T cells	Infiltration of activated macrophages/T cells in the brain parenchyma a	WM lesions	Neuroinflammation	Diffuse Demyelination	[60]
		Neurons	AMPAR/NMDAR Overexpression	Neuronal Excitotoxicity	Neurodegeneration	Severe Disease Symptoms	[78]
	EAE TNF KO mice	Macrophages, T cells, Neurons, Glial cells	Infiltration reduction by macrophages and T cells; No AMPAR/NMDAR Overexpression; Enhanced Tregs cells	Neuronal homeosasis	Neuroprotection	Severe Disease Symptoms	[68]
	EAE TNFR1 KO mice	Macrophages, T cells, Neurons, Glial cells	No AMPAR/NMDAR OverexpressionEnhanced Tregs cells	Remyelination Increase and Neurodegeneration Reduction	Neuroprotection	Reduction of disease signs and clinical symptoms	[69]
	EAE TNFR2 KO mice	T regs	Suppression of T_{regs} in response to autoreactive T cells	Impaired Remyelination	Demyelination	Aggressive Disease	[75, 76]
		Oligodendrocytes	Oligodendrocytes Death	Impaired Remyelination	Demyelination	Severe Disease Symptoms; Enhanced T cells infiltration in the CNS; Diffuse Demyelination	[69, 83]

Therefore, the detection of TNF and its receptors serum levels may be useful in assessing the pharmacological efficacy of DMTs in PIRA.

Conclusions and perspectives

The impact of TNF on MS involves intricate molecular processes, and understanding these mechanisms is essential for improving treatment strategies and assessment for PIRA. Specifically, a receptor-selective modulation of the TNF signal pathway could provide a novel therapeutic strategy to attenuate the progression of disability independent of relapse activity in RRMS. However, this topic requires further research to fully grasp the potential therapeutic implications. This promising field of study could enhance the quality of life for people with MS.

Abbreviations

TNF	Tumor necrosis factor
MS	Multiple sclerosis
PIRA	Progression independent of relapse activity
CNS	Central nervous system
RRMS	Relapsing–remitting MS
SPMS	Secondary progressive MS
PPMS	Primary progressive MS
PrMS	Progressive MS
GM	Grey matter
EDSS	Expanded disability status scale
WM	White matter
CALs	Chronic active lesions
CSF	Cerebrospinal fluid
TNFR	TNF receptor
TNFR1	TNF receptor type-1

TNFR2	TNF receptor type-2
TACE	TNF converting enzyme
mTNF	Transmembrane TNF
sTNF	Soluble TNF
Th	T helper
TRADD	TNFR1-associated death domain
FADD	Fas-associated death domain
RIPK	Receptor-interacting serine/threonine-protein kinase
MLKL	Mixed lineage kinase domain-like pseudokinase
TRAF2	TNFR-associated factor 2
JNK	C-Jun-N-terminal kinase
ERK	Extracellular signal-regulated kinase
NFκB	Transcription factor nuclear factor-κB
EAE	Experimental autoimmune encephalomyelitis
WT	Wild type
KO	Knockout
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
NMDA	N-methyl-D-aspartate
DMTs	Disease-modifying treatments
sNfLs	Serum neurofilament light chain
GA	Glatiramer acetate
DC	Dendritic cell

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
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Competing interests
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