Tumor necrosis factor superfamily in multiple sclerosis: from pathology to therapeutic implications

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ABSTRACT

Tumor necrosis factor (TNF) is a key player in multiple sclerosis pathology. TNF signaling is dually regulated by antagonist groups of actors: TNFR1, mediating proinflammatory effects and synaptopathy, CD40L-CD40 dyad, crucial for blood-brain barrier breakdown and facilitation of recruitment of inflammatory cells in the central nervous system, and TNFR2, promoting neuroprotective and reparative functions. A promising therapeutic approach in multiple sclerosis is represented by selective TNFR1 antagonists and TNFR2 agonists, possibly in combination. TNFR2 agonists could exert both central effects such as remyelination, reduction of glutamatergic excitotoxicity, and peripheral immunomodulation by enhancing T cells (Treg) activity. On the other side, the potential therapeutic role of platelet and CD40L-CD40 dyad inhibition could be beneficial to preserve blood-brain barrier integrity and thereby dampen neuroinflammation.

INTRODUCTION

Multiple sclerosis (MS) is a neuroimmunological disease affecting mainly young adults. Cytokines dysregulation plays a relevant role in MS pathology. One major actor is the tumor necrosis factor (TNF), a pleiotropic cytokine involved in many physiological and pathological functions both in the immune system and in the central nervous system (CNS). In MS, TNF could alternatively play neuroinflammatory or neuroprotective effects due to the high complexity of its signaling pathways and the presence of specific interactions with other cytokines, CNS cells, or immune cells.[1]

TUMOR NECROSIS FACTOR SUPERFAMILY AND BIOLOGICAL FUNCTION

TNF is the prototype of the TNF superfamily, exerting several biological functions. There are two distinct surface TNF receptors (TNFR): the TNFR superfamily member 1A (TNFR1) and TNFR superfamily member type 2 (TNFR2).[2] TNFR1 and TNFR2 play opposite immunological functions. TNFR1, which is widely expressed, plays a role in tissue degeneration and inflammation, while TNFR2 is selectively expressed in

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Citation: Azzolini F, Bruno A, Dolcetti E, et al. Tumor necrosis factor superfamily in multiple sclerosis: from pathology to therapeutic implications. Bleeding, Thrombosis, and Vascular Biology 2023;2:66.

Key words: TNF; multiple sclerosis; synaptopathy; TNFR1; TNFR2.

Contributions: DC, FA, conceptualization; FB, FA, methodology, writing, original draft preparation; AB, ED, DC, resources; DC, writing, review and editing, project administration. All authors have read and agreed to the published version of the manuscript.

Conflict of interest: the authors declare the following potential conflicts of interest for the research, authorship, and/or publication of this article. FB acted as an advisory board member of Teva and Roche and received honoraria for speaking or consultation fees from Merck Serono, Teva, Biogen Idec, Sanofi, and Novartis and non-financial support from Merck Serono, Teva, Biogen Idec, and Sanofi. DC is an advisory board member of Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva. He is also the principal investigator in clinical trials for Bayer Schering, Biogen, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, and Teva. His preclinical and clinical research was supported by grants from Bayer Schering, Biogen Idec, Celgene, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. FA, AB, and ED declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding: none.

Ethics approval and consent to participate not applicable.

Acknowledgments: this manuscript is based on an invited presentation at the 9th Roberto Lorenzet Memorial "L'infiammazione base comune delle malattie cronico-degenerative", held on January 13, 2023 - Pozzilli (IS, Italy).

Received: 8 March 2023.
Accepted: 14 April 2023.

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Bleeding, Thrombosis and Vascular Biology 2023; 2:66
doi:10.4081/btvb.2023.66

neurons, microglia, oligodendrocytes, T cells, and endothelial cells, mediating homeostatic functions.

Another key player of the TNF superfamily is the CD40-CD40L dyad, an immune checkpoint regulator.

TNF has a key role in the systemic inflammatory response, immune surveillance, and immunological homeostasis. Moreover, it regulates many aspects of T cell biology. TNF-TNFR2 signaling seems to prevail in a subset of T cells (Treg) that show immunoregulatory functions, while TNFR1 is mainly involved in the activation of CD4+ and CD8+ T cell apoptosis and proinflammatory activities. TNFR1 and TNFR2 also play opposite roles in MS, the first exerting proinflammatory effects, and the second neuroprotective and reparative functions.[1,3] Several experimental and pathological studies suggested that the CD40-CD40L activation has a central role in the inflammatory response underlying MS, especially in blood-brain barrier (BBB) disruption.[4]

In CNS, TNF is constitutively expressed at low levels and is mainly produced by microglia, astrocytes, and glial cells. In a healthy brain, TNF exerts regulatory functions. Moreover, it acts as a physiological gliotransmitter and synaptic mediator, as in the regulation of surface expression of AMPA receptors.[5] However, the homeostatic functions of TNF could turn into pathological effects under proinflammatory conditions.[1,3]

TUMOR NECROSIS FACTOR SUPERFAMILY INVOLVEMENT IN EXPERIMENTAL MODELS AND HUMAN MULTIPLE SCLEROSIS

Experimental animal models showed that the TNFR1 pathway can enhance glutamate excitotoxicity, neuroinflammatory response, BBB permeability, and oligodendrocytes apoptosis.[1]

CD40-CD40L dyad also promotes neuroinflammation: soluble CD40L is mainly derived from platelets, which are also important players in disease pathogenesis. Indeed, MS patients exhibit chronic platelet activation, and elevated platelet adhesion is evident during the initial stage of MS.[6] The platelet CD40L-mediated activation of CD40 induces the expression of inflammatory mediators, such as cytokines and chemokines, that enhance BBB disruption and neuro-inflammation.[4]

On the contrary, TNFR2 signaling reduces excitotoxicity and promotes remyelination in CNS. In experimental autoimmune encephalitis (EAE) mice models, the selective ablation of TNFR2 in oligodendrocytes induced lower remyelination, higher oligodendrocyte loss, increased autoreactive cells infiltrate,[1,7] more severe disease course, and increased BBB permeability.[1] To notice, TNFR2 ablation in peripheral monocytes/macrophages resulted in impaired systemic immunity, milder disease course, lower demyelination, and CNS T cell infiltration,[8] demonstrating an opposite role of TNFR2 in the periphery *versus* CNS.

The dual role of TNF is also supported by experimental pharmacological studies. For example, both in EAE and demyelination cuprizone models, the selective inhibition of TNFR1 induced milder disease progression, reduced disease severity and inflammatory infiltrates, lower rates of demyelination and axonal damage, and resolved microgliosis. According to the hypothesis of an opposite role of TNFR2 signaling, the potentiation of TNFR2 with fusion proteins showed a better disease course in EAE.[1] Moreover, in cuprizone models, TNF-KO mice demyelination was similar to wild-type mice. However, TNFR2-deficient but not TNFR1-deficient mice failed to remyelinate compared to wild-type mice.[9]

Finally, interesting data revealed that the platelet-CD40L axis could be a potential pharmacological target in MS: both genetic deficiency and antibody-mediated inhibition of the CD40–CD40L dyad, in fact, reduced disease severity in EAE.[4] Moreover, intracerebroventricular injection of platelet-derived growth factor CC (PDGF-CC) induced upregulation, whereas blocking PDGF-CC during EAE led to downregulation of TNFα and interleukin 1α (IL1A) at the BBB.[10] Finally, oral administration of low-dose acetylsalicylic acid resulted in milder EAE, reduced inflammatory infiltrates, and demyelination.[11]

TNF in MS human *post-mortem* studies demonstrated higher TNF levels in active MS lesions, with transcriptional upregulation both of TNFR1 and TNFR2. However, a higher expression of TNFR1-mediated necroptosis was observed, demonstrating the predominance of TNFR1 in destructive effects. On the contrary, several studies suggested that the increased expression of TNFR2 is linked to reparative effects.[1] TNF was also studied *in vivo* in MS subjects both in serum and in cerebrospinal fluid (CSF) samples. Higher levels of TNF were found in subjects with progressive MS (PMS) with severe disease progression, in primary PMS, in active relapsing-remitting MS (RRMS), while TNF had a negative correlation with cognitive decline in RRMS.[1,12]

Other studies showed that higher CSF TNF concentrations were associated with neurological deficits and with the degree of disease progression in PMS, whereas serum TNF levels did not reach this association.[13] Moreover, in MS subjects, CD4+TNF+T cells were found at higher concentrations in CSF compared to peripheral blood.[14] These data suggest a specific intrathecal synthesis of TNF by autoreactive T cells.

As mentioned before, TNF could exert excitotoxic damage in MS, leading to axonal, oligodendroglial, as well as synaptic pathology in MS. In a recent study, for example, T cells isolated from the serum of RRMS patients and incubated in mice brain slices were able to induce synaptic alterations only if derived from MS patients

with active inflammation. In the same model, the coincubation of T cells with a TNF antagonist (etanercept) prevented synaptopathy.[15] These data confirm that TNF mediates glutamatergic excitotoxicity in MS.

Important considerations are also derived from the effects of non-selective anti-TNF drugs both on MS patients and on patients with systemic autoimmune diseases such as psoriasis and rheumatoid arthritis. In the first group of patients, the use of anti-TNF medications had negative effects, escalating inflammation and the severity of the illness. Moreover, in patients treated with infliximab, etanercept, or adalimumab for systemic autoimmune diseases new-onset demyelinating lesions or clinical symptoms fulfilling definite MS criteria are sometimes observed.[1] These effects could be explained by the non-selective antagonism of these drugs on TNFR1 and TNFR2 pathways, and then on the inhibition of the anti-inflammatory TNFR2 signaling.

CONCLUSIONS

TNF is a key player in MS pathology, as confirmed by several preclinical models and clinical studies. In a quite simplistic way, it is possible to affirm that TNF signaling is dually regulated by antagonist groups of actors: TNFR1, mediating proinflammatory effects and synaptopathy, CD40L-CD40 dyad, crucial for BBB breakdown and facilitation of recruitment of inflammatory cells in CNS, and TNFR2, promoting neuroprotective and reparative functions.

Therefore, a promising therapeutic approach in MS is represented by the use of selective TNFR1 antagonists and TNFR2 agonists, possibly in combination. TNFR2 agonists, interestingly, could exert both central effects such as remyelination, reduction of glutamatergic excitotoxicity, and peripheral immunomodulation by enhancing Treg activity. On the other side, the potential therapeutic role of platelet and CD40L-CD40 dyad inhibition could be beneficial to preserve BBB integrity and thereby dampen neuroinflammation.

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