McKarns SC* and Moisson FE

1Department of Microbiology and Immunology, University of Missouri, Columbia, MO 65212, USA
2Laboratory of TGF-β Biology, Epigenetics, and Cytokine Regulation, Center for Cellular and Molecular Immunology, Department of Surgery, University of Missouri School of Medicine, Columbia, MO 65212, USA

Keywords: TNFR2; CNS Demyelination; Autoimmunity; Gender; Sex; Microbiome

Tumor necrosis factor-α (TNF), a double-edged sword with both pro-inflammatory and anti-inflammatory properties, is one of the most widespread clinically targeted cytokines [1-4]. Anti-TNF therapies, such as infliximab, adalimumab, golimumab, and certolizumab, are central to the treatment of several autoimmune diseases, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), ankylosing spondylitis (SpA), and psoriasis. TNF blockade may also offer a potential avenue for the treatment of acute neuromyelitis optica (NMO) and/or NMO spectrum disorders (NOMS) [5]. However, the use of currently available anti-TNF therapies is limited by their association with new onset or exacerbation of neuroinflammatory demyelinating disorders, including multiple sclerosis (MS), optic neuritis (ON), and acute transverse myelitis [2]. The precise mechanisms that predispose patients who receive anti-TNF treatment to benefit or increase risk of central nervous system (CNS) demyelination are not well-understood, but several theories have been proposed. First, TNF blocking agents may not penetrate the endothelial blood brain barrier (BBB), but rather precipitate disease by augmenting peripheral T cell auto-reactivity [6,7]. Second, TNF blockade may skew cytokine production, i.e., decrease IL-10 and increase IL-12 production, to facilitate demyelination [8]. Third, TNF blockers may “sponge” and thus lower the level of TNF in the periphery, thereby restricting disease alleviation to organs outside of the CNS. And fourth, reduced peripheral TNF levels may unmask a latent infection to propagate an autoimmune process [9]. The objective of this commentary is to bring to the forefront an alternative theory that highlights the influence of the gut microbiome on not only development but also treatment of autoimmune diseases [10].

The multiplicity of effects that TNF imparts on immunological responses, such as host defense, inflammation, cell death, and tissue repair, emanate from a two-ligand, two-receptor signaling system as well as differential expression of both ligands and their receptors. This pleotropic cytokine is produced mostly by monocytes and macrophages, but also lymphoid cells, microglia, astrocytes, dendritic cells, natural killer cells, and others. TNF is synthesized as a monomeric transmembrane molecule (tmTNF) and is cleaved from the cell surface by TNF converting enzyme (TACE) to release a soluble form of TNF (sTNF). HomotrimERIC TNF (tmTNF and sTNF) binds to one of two distinct receptors, type I TNF receptor (TNFR1) or type 2 TNF receptor (TNFR2). TNFR1 is ubiquitously expressed and is activated in response to sTNF to promote inflammation, apoptosis, and demyelination. In contrast, TNFR2 expression is largely restricted to endothelial, hematopoietic, microglial, and some neuronal cells; has a higher affinity for tmTNF than sTNF; promotes cell survival; CD4+ Foxp3+ T regulatory (Treg) cell expansion; oligodendrocyte regeneration; and nerve remyelination [4,11-13]. Additionally, the gene for TNF is linked to the human major histocompatibility complex (MHC) located on chromosome 6 and TNFRSF1A, encoding TNFR1, is recognized as a risk allele for MS [14,15]. Animal models of experimental autoimmune encephalomyelitis (EAE) have associated TNFR1 and TNFR2 deficiency with decreased and increased disease severity, respectively, to suggest a selective role for TNFR1 in CNS demyelination. Thus, selective inhibition of sTNF/TNFRI signaling, leaving beneficial tmTNF/TNFRI signaling intact may open new opportunities for TNF-selective

next-generation therapeutics for the prevention and/or treatment of CNS autoimmune disorders (Figure 1).

Previous studies in mice have revealed that CD4+ T cell–intrinsic TNFR2 promotes IL2 expression [16]. Given that IL-2 is required for the expansion and function of CD4+ FoxP3+ T cells (Tregs), Miller et al., used a genetic loss-of-function approach to determine whether selective ablation of TNFR2 is sufficient to augment MOG-specific CD4+ T cell auto-reactivity [10]. Surprisingly, 59 of 64 (92%) of female, but only 5 of 60 (8%) of male, C57BL/6J TNFR2−/− 2D2 Foxp3+ reporter mice developed fulminant spontaneous autoimmune disease. A similar increase in spontaneous disease incidence was not observed in female TNFR2−/− that did not carry the 2D2 T cell receptor transgene. While a clear understanding of the underlying mechanisms remain elusive, these results are consistent with the view that anti-TNF therapy exacerbates risk in those patients who are already at risk (due to a genetic predisposition) for developing immune-mediated demyelination [17]. Augmented disease was also absent in TNF−/− 2D2 mice to implicate distinct roles for TNFR1 and TNFR2. Histologically, lesions were absent from the brain, but the optic nerves and spinal cord exhibited extensive inflammation, demyelination, and axonal loss, with infiltration of predominantly B cells and T cells. With the noted exception of high-titer of MOG antibodies, the disease is highly reminiscent of NMO-like pathology. Importantly, it has yet to be determined whether the presence of MOG antibodies in TNFR2−/− 2D2 mice reflect an underlying pathogenic mechanism, a secondary immune response, a simple bystander phenomenon, or even a beneficial effect.

Strikingly, maternal antibiotic treatment protected TNFR2−/− 2D2 offspring from developing spontaneous disease. The microbiome, consisting of the trillions of microorganisms (bacteria, viruses, and fungi) residing in our bodies, is a rapidly emerging area of interest in the medical community. While most microorganisms in our microbiome are beneficial or harmless, changes in the microbiome (dysbiosis) have been linked to diseases, including type 1 diabetes (T1D) and IBD [18,19]. To explore the possible connection between changes in the microbiome and female-biased spontaneous disease development in TNFR2−/− 2D2 mice, the Miller et al., first demonstrated that cross-fostering of TNFR2−/− 2D2 pups from the birth (donor) to recipient wild-type mothers, completely devoid of antibiotic treatment, restored disease susceptibility in female TNFR2−/− 2D2 mice. Data was then collected on the composition of gut microbiome in male and female TNFR2−/− 2D2 and TNFR2−/− mice. 16S RNA gene amplicon sequencing of fecal samples identified a distinct gut microbiota profile, including a higher abundance of Akkermansia muciniphila, Sutterella

*Corresponding author: Susan C. McKarns, Department of Surgery, University of Missouri School of Medicine, M616 Medical Sciences Building, Columbia, MO 65212. E-mail: mckarns@health.missouri.edu

Received April 25, 2016; Accepted May 03, 2016; Published May 10, 2016

Citation: McKarns SC, Moisson FE (2016) TNF Blockade, CNS Autoimmunity, Sex, and the Microbiome. J Mult Scler (Foster City) 3:172. doi:10.4172/2376-0389.1000172

Copyright: © 2016 McKarns SC, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
sp., Oscillospira sp., Bacteroides acidifaciens, and Anaeroplasma sp. in male TNFR2−/− 2D2 mice that associated with disease protection. These results strongly implicate that interactions between environmental (e.g., TNF-α) in mouse microbiota contribute to the development of spontaneous disease in female TNFR2−/− 2D2 mice. Importantly, these observations highlight the importance of the microbiome on not only development but also treatment of autoimmune disease. Male-biased microbiome-mediated protection has also been implicated in disease progression in the NOD T1D mouse model [20]. Collectively, the TNFR2−/− 2D2 model raises an interesting question of whether anti-TNF treatment may be linked to myelin-specific or cross-reactivity to environmental myelin-similar peptides (commensal bacteria), in AQ4-IgG seronegative, MOG-IgG seropositive NMO and/or NMO spectrum disorder patients [21-23].

In conclusion, experimental models and clinical trials suggest a role for TNF blockade with CNS demyelination. The potential for sTNF and tmTNF to exert different functions in different cells under normal and pathological conditions within the CNS has warranted investigations to delineate the distinct functions of these two ligands. The report by Miller et al., identifying gut microbiota as a putative TNFR2-selective factor that affects autoimmune disease development in genetically susceptible animals, is consistent with the idea that selective targeting of TNFR1-mediated signaling, while sparing TNFR2 activation, may lessen adverse effects of anti-TNF therapies in the CNS. The findings in this report further suggest that investigations aimed to better understand distinct sTNF and tmTNF functions should be extended to include the intestines and the composition of commensal microbiota. Lastly, this report highlights that individuals may respond differently to anti-TNF therapy, in part, because of the commensal microbes that they carry, and further emphasizes the importance of sex and gender when studying mechanisms by which TNF blockade may affect health and disease processes.

(Figure 1). Shedding is an important for the control of TNFR1 and TNFR2 activity. There are two forms of tumor necrosis factor-α (TNF), a membrane-bound protein (tmTNF) and a soluble form (sTNF). sTNF is generated by cleavage of tmTNF by the metalloproteinase, TACE (TNF converting enzyme), alternatively called ADAM 17 (adisintegrin and metalloproteinase), from the cell membrane. TNF mediates its pleoptropic functions through two distinct receptors. Type 1 TNF receptor (TNFR1) expression is ubiquitous and largely constitutive. In contrast, type 2 TNF receptor (TNFR2) expression is more restricted to cells of the immune system, such as B and T lymphocytes (especially CD4+FoxP3+ T regulatory cells), macrophages, but also epithelial cells of the gut, microglia, and neurons. Like tmTNF, TNFR1 and TNFR2 are shed from the cell surface by TACE/ADAM17 and released into the extracellular compartment. tmTNF bind and signals through TNFR2 with higher affinity than TNFR1; whereas, sTNF has a higher affinity for TNFR1 than TNFR2. Soluble Lymphotoxin-a (LT-α), also called TNF-β, binds TNFR1 and TNFR2 with comparable affinity.

References
1. Probert L (2015) TNF and its receptors in the CNS: The essential, the desirable and the deleterious effects. below Neuroscience 302: 2-22.


