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TNF Blockade, CNS Autoimmunity, Sex, and the Microbiome

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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 (NMOSD) [5]. However, the use of currently available anti-TNF therapeutics 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 1 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/TNFR1 signaling, leaving beneficial tmTNF/TNFR2 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_{35-55}-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 $Foxp3^{gfp}$ 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 rRNA gene amplicon sequencing of fecal samples identified a distinct gut microbiota profile, including a higher abundance of *Akkermansia muciniphila*, *Sutterella*

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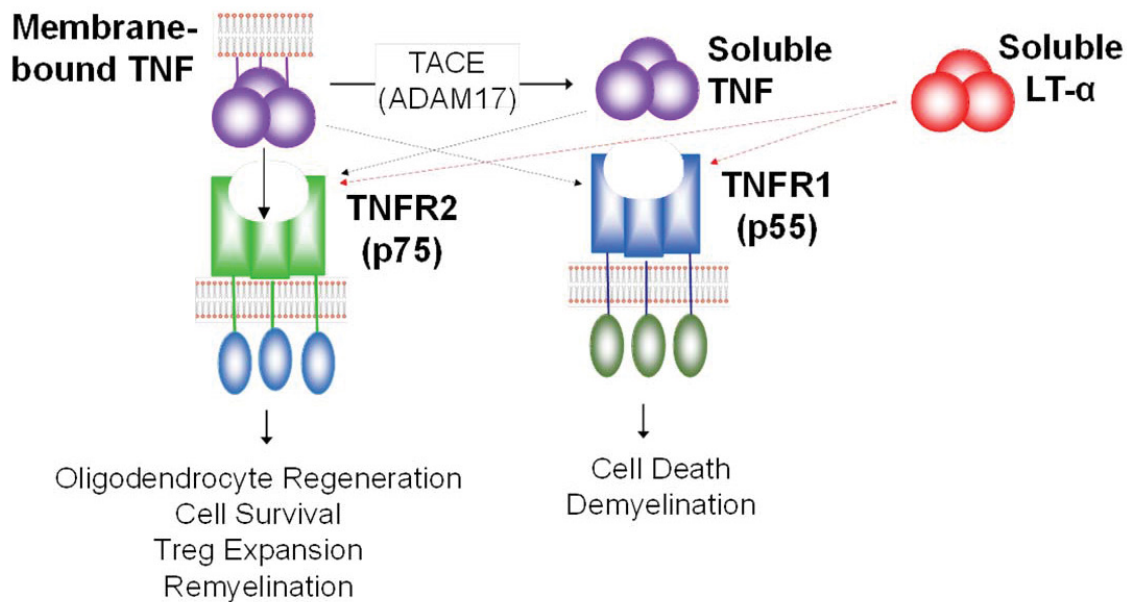

Figure 1: Shedding is an important for the control of TNFR1 and TNFR2 activity.

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., TNFR2 signaling blockade and sex hormones) and genetic factors (e.g., 2D2 auto-reactivity) with gut 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 AQP4-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 in 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 andmetalloproteinase), 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.

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