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REVIEW

TNF AND ITS RECEPTORS IN THE CNS: THE ESSENTIAL, THE DESIRABLE AND THE DELETERIOUS EFFECTS

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Abstract—Tumor necrosis factor (TNF) is the prototypic pro-inflammatory cytokine. It is central to host defense and inflammatory responses but under certain circumstances also triggers cell death and tissue degeneration. Its pleiotropic effects often lead to opposing outcomes during the development of immune-mediated diseases, particularly those affecting the central nervous system (CNS). The reported contradictions may result from lack of precision in discussing TNF. TNF signaling comprises at minimum a two-ligand (soluble and transmembrane TNF) and two-receptor (TNFR1 and TNFR2) system, with ligands and receptors both differentially expressed and regulated on different cell types. The ''functional multiplicity'' this engenders is the focus of much research, but there is still no general consensus on functional outcomes of TNF signaling in general, let alone in the CNS. In this review, evidence showing the effects of TNF in the CNS under physiological and pathophysiological conditions is placed in the context of major advances in understanding of the cellular and molecular mechanisms that govern TNF function in general. Thus the roles of TNF signaling in the CNS shift from the conventional dichotomy of beneficial and deleterious, that mainly explain effects under pathological conditions, to incorporate a growing number of ''essential'' and ''desirable'' roles for TNF and its main cellular source in the CNS, microglia, under physiological conditions including regulation of neuronal activity and maintenance of myelin. An improved holistic view of TNF function in the CNS might better reconcile the expansive experimental data with stark clinical evidence that reduced functioning of TNF and its dominant pro-inflammatory receptor, TNFR1, are risk factors for the development of multiple sclerosis. It will also facilitate the safe translation of basic research findings from animal models to humans and propel the development of more selective anti-TNF therapies aimed at selectively inhibiting deleterious effects of this cytokine while maintaining its essential and desirable ones, in the periphery and the CNS.

Key words: TNF, neurodegeneration, inflammation, multiple sclerosis, therapy, microglia.

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INTRODUCTION

At the grand age of thirty since its isolation and cloning, tumor necrosis factor (TNF, originally cachectin or TNF-α) (Pennica et al., 1984; Wang et al., 1985; Aggarwal et al., 1985) is the name-giving cytokine to a large ligand superfamily and maintains its position as one of the most intensively studied molecules in the field of biomedical research. It was originally identified as a blood factor causing hemorrhagic necrosis of certain tumors (Carswell et al., 1975; Ruff and Gifford, 1981) and a macrophage factor responsible for disease-associated wasting and lethal shock (Rouzer and Cerami, 1980; Kawakami and Cerami, 1981; Beutler et al., 1985). Intensive multidisciplinary research into the biological functions and therapeutic applications of TNF has revealed fine details of its functional multiplicity and complexity of action. Its functions in the central nervous

Abbreviations: AD, Alzheimer's disease; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid receptor; BBB, blood–brain barrier; CNS, central nervous system; DR, death receptor; EAE, experimental autoimmune encephalomyelitis; FADD, Fas-associated death domain; HD, Huntington's disease; LPS, lipopolysaccharide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; PD, Parkinson's disease; pMCAO, permanent middle cerebral artery occlusion; solTNF, soluble TNF; tmTNF, transmembrane TNF; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand.

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system (CNS) are, however, still incompletely understood and this represents one important limitation for the safe therapeutic targeting of TNF in human disease.

TNF is primarily an innate immune defense molecule important in the maintenance of homeostasis at the cellular, tissue and organism levels (Vassalli, 1992). Studies in mice showed that it is not necessary for normal development but is required for proper lymphoid organ organization and function and for host defense responses against pathogens (Pasparakis et al., 1996), (Marino et al., 1997). It is rapidly produced in response to stimuli, mainly by activated macrophages and monocytes, and also by many other cell types, and orchestrates an inflammatory response that is central to successful innate immune responses ultimately clearing pathogens and initiating healing processes. The potent pro-inflammatory properties of TNF require that its production and activity be kept under tight temporal and spatial control. As we will see in more detail below, multiple checkpoints are in place to ensure that the effects of TNF are limited to acute responses, including regulation of *Tnf* gene expression at transcriptional and translational levels, and the regulated shedding of TNF (Black, 2004; Mohammed et al., 2004) and its receptors (Porteu and Hieblot, 1994) in response to various agonists. Elaborate control mechanisms also operate at the level of TNF receptor signaling so that TNF receptor 1 (TNFR1), which signals most TNF's effects including inflammation and cell death, induces pathways that appear to be hierarchically layered to control cell fate after ligand binding, with induction of gene transcription and pro-survival pathways through NF-κB transcriptional activity protecting against apoptosis, and caspases in turn protecting against necrosis. Disturbances at any point in the delicate web of control mechanisms governing TNF function caused by environmental or genetic factors can result in pathology. This is aptly demonstrated at the clinical level by the TNFR1-associated periodic syndromes (TRAPS), which are caused by TNFR1 mutations that reduce receptor cleavage resulting in increased TNF signaling and systemic autoinflammatory pathology (McDermott et al., 1999), as well as cases of CNS involvement (Minden et al., 2004).

TNF is the prototypic pro-inflammatory cytokine. Soon after its discovery, aberrant TNF production was found to trigger inflammatory pathologies such as rheumatoid arthritis, insulitis and inflammatory bowel disease in experimental animals (Keffer et al., 1991; Picarella et al., 1993; Kontoyiannis et al., 1999), and to be a characteristic of diverse diseases in the periphery and CNS of humans that involve inflammation, including sepsis, chronic immune and autoimmune pathologies, neurodegeneration and cancer (Vassalli, 1992). It was quickly recognized as an important therapeutic target, and today TNF inhibitors represent blockbuster drugs for the treatment of a variety of chronic immune diseases in the periphery, notably rheumatoid arthritis, psoriasis and inflammatory bowel disease. However, shadowing the spectacular success of non-selective TNF inhibitors are serious side effects associated with immune suppression, especially increased risk of infections; tuberculosis, bacterial sepsis and invasive fungal infections; as well as of lymphoma and other malignancies in children and adolescents (Kontermann et al., 2009). Entirely unexpected at the time, was the finding that TNF inhibitors exacerbated multiple sclerosis (MS), a common inflammatory demyelinating disease of the central nervous system (CNS), when tested in clinical trials in MS patients (van Oosten et al., 1996; Multiple Sclerosis Study Group, 1999), and even induced new cases of demyelinating disease and neuropathies in patients treated for other diseases (Stubgen, 2008; Bosch et al., 2011). These clinical data provided the first and most convincing evidence that TNF, further to having pro-inflammatory effects, exerts essential beneficial functions in the CNS and that such effects would need to be understood and taken into consideration so that safer TNF-targeted therapies could be developed, and if possible applied to inflammatory CNS diseases.

TNF AND TNF RECEPTORS

The pleiotropic effects of TNF reflect its complex signaling mechanisms, which are the subject of excellent reviews and will not be detailed here (Wallach et al., 1999; Wajant et al., 2003; Vanden Berghe et al., 2014). TNF is produced in two bioactive forms: transmembrane TNF (tmTNF), which acts by cell-to-cell contact, and soluble TNF (solTNF), which is released following regulated cleavage of tmTNF (Kriegler et al., 1988) by TNFα-converting enzyme (TACE/ADAM17) (Black et al., 1997; Moss et al., 1997). Studies in transgenic mice have been instrumental for defining essential functions of TNF and its receptors in health and disease (Table 1). They showed that tmTNF and solTNF have distinct functions with tmTNF mediating a subset of beneficial TNF activities while lacking the systemic inflammatory effects of solTNF. Mice deficient in TNF, which are therefore deficient in both solTNF and tmTNF, lack normal secondary lymphoid organ structure, fail to form germinal centers upon immunization and are unable to mount host defense responses to infections (Pasparakis et al., 1996; Marino et al., 1997), or optimal inflammatory responses in models of autoimmunity such as experimental autoimmune encephalomyelitis (EAE) (Korner et al., 1997b), a widely-used model for immune pathology in MS. By contrast, mice deficient in solTNF, but producing functional uncleavable tmTNF, show partially restored lymphoid organ structure and function (Ruuls et al., 2001; Alexopoulou et al., 2006), control *Leishmania major* infection (Allenbach et al., 2008) and partially control intracellular bacterial infections (Torres et al., 2005; Alexopoulou et al., 2006; Musicki et al., 2006; Olleros et al., 2012), suggesting that tmTNF is sufficient for basic host defense responses, while solTNF is necessary for optimizing them. Importantly, tmTNF was not sufficient for the development of the inflammatory responses necessary for EAE and a model of arthritis to develop (Ruuls et al., 2001; Alexopoulou et al., 2006). These early findings were the first to support the hypothesis that selective targeting of solTNF might offer significant advantages over non-selective blockade of TNF for the treatment of chronic inflammatory diseases including those in the CNS, by inhibiting overt inflammation while