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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.

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

Contents

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

Table 1. Main characteristics and CNS effects of mice with targeted deficiencies in TNF and TNF receptors

Murine gene disrupted	Main characteristics	References
Tnf deletion	Deficient in solTNF & tmTNF	
	- Resistance to LPS-induced shock; increased susceptibility to infections with *Listeria monocytogenes* and *Candida albicans*; lack splenic primary B cell follicles; cannot form follicular dendritic cell networks and germinal centres	Pasparakis et al. (1996) Marino et al. (1997)
	- Reduced OPC and remyelination in MS model	Arnett et al. (2001)
	- Increased lesions in cerebral ischemia model	Lambertsen et al. (2009)
	- Delayed EAE onset & lymphocyte infiltration of CNS, enhanced severity of chronic disease	Korner et al. (1997a,b) Frei et al. (1997) Liu et al. (1998) Kassiotis and Kollias (2001)
Tnf Δ1–9 K11E (uncleavable tmTNF knockin)	Deficient in solTNF	
	- Resistance to LPS-induced shock; improved lymphoid organ structure compared to *Tnf* deletion; resistance to EAE	Ruuls et al. (2001)
Tnf Δ1–12 (uncleavable tmTNF knockin)	Deficient in solTNF	
	- Resistance to LPS-induced shock; like *Tnf*−/− mice, lack splenic primary B cell follicles; cannot form follicular dendritic cell networks and germinal centres.; resistance to *Listeria monocytogenes*; resistance in arthritis and EAE models	Alexopoulou et al. (2006)
Tnfrsf1a deletion	Deficient in TNFRI	
	- Resistance to LPS-induced shock; increased susceptibility to *Listeria monocytogenes*; resistance to lethal LPS doses	Rothe et al. (1993) Pfeffer et al. (1993)
	- Increased lesions in cerebral ischemia model	Gary et al. (1998) Taoufik et al. (2007)
	- Increased hippocampal neuron death in epilepsy model	Lambertsen et al. (2009)
	- Reduced pathology in retinal ischemia and AD models	Fontaine et al. (2002) He et al. (2007)
	- Delayed EAE onset	Suvannavejh et al. (2000) Eugster et al. (1999) Kassiotis and Kollias (2001)
Tnfrsf1b deletion	Deficient in TNFRII	
	- Increased serum TNF; increased resistance to TNF-induced cell death and tissue necrosis	Erickson et al. (1994) Peschon et al. (1998)
	- Reduced OPC proliferation and remyelination in MS model	Arnett et al. (2001)
	- Increased sensitivity of cortical neurons to glutamate excitotoxicity *in vitro* and increased pathology in retinal ischemia model *in vivo*	Marchetti et al. (2004) Fontaine et al. (2002)
	- Increased EAE severity	Eugster et al. (1999)

maintaining host defense and possibly other beneficial mechanisms.

Additional layers of complexity are present at the level of intracellular TNF signaling. TNF signals through two distinct cell-surface high-affinity receptors, TNFR1 (CD120a, 55 kDa; encoded by *TNFRSF1A*) and TNFR2 (CD120b, 75 kDa; encoded by *TNFRSF1B*), which are the founding members of the TNFR superfamily. tmTNF signals efficiently through TNFR1 and 2, while solTNF selectively signals through TNFR1, leaving tmTNF as the main TNFR2 ligand (Grell et al., 1995). TNFR1 is ubiquitously and constitutively expressed and shows highly complex signaling pathways. Briefly, TNFR1 engagement leads to the recruitment of TRADD (TNFR1-associated death domain protein), which acts as a platform for various signaling complexes that are involved in two diametrically opposed outcomes; cell survival and death. TNFR1 is a member of the death receptor family (DR) because it has an intracellular death domain sequence and can induce apoptosis in sensitized cells by the recruitment of FADD (Fas-associated death domain protein) and caspase 8 to TRADD through homotypic death domain interactions (Wallach et al., 1999; Wilson et al., 2009). However, TNFR1 is not cytotoxic to most cells and induces direct pro-inflammatory signaling through the formation of a membrane-associated protein complex (complex I). Here, TRADD recruits TRAF2 (TNFR-associated factor 2), RIP-1 (receptor-interacting protein-1), cellular inhibitor of apoptosis protein-1 or -2 (cIAP-1, cIAP-2) and LUBAC (linear ubiquitin chain assembly complex), and favors activation of proinflammatory signals through the transcription factors NF-κB and AP-1 (Micheau and Tschopp, 2003; Walczak, 2011). NF-κB induces transcription of many genes including those encoding proinflammatory cytokines, chemokines and antiapoptotic factors such as cIAP1/2, Bcl-2, Bcl-xL and c-FLIP (cellular FLICE-inhibitory protein)(Wajant et al., 2003). Activation of NF-κB is therefore a primary mechanism of cell protection against death stimuli; the switch to cell death follows destabilization of complex I, e.g. by blockade of protein synthesis or of NF-κB activity (Baud and Karin, 2001; Karin and Lin, 2002) and formation of a cytosolic complex II which signals cell death (Wallach et al., 1999; Micheau and Tschopp, 2003). In line with the primary role of TNF as a defense molecule, TNFR1 controls defense at the cellular level, by inducing death of damaged, infected cells, at the tissue level by orchestration of the inflammatory response, and at the organism level by inducing changes such as fever and sleep. Indeed, similar to TNF knockout mice deficient in

both solTNF and tmTNF (Pasparakis et al., 1996), and tmTNF knockin mice deficient only in solTNF (Ruuls et al., 2001; Alexopoulou et al., 2006), TNFR1 knockout mice show reduced inflammatory responses. Also, similar to TNF knockout mice (Pasparakis et al., 1996), but unlike tmTNF knockin mice (Ruuls et al., 2001; Alexopoulou et al., 2006), TNFR1 knockout mice show reduced defense against the intracellular pathogen *Listeria monocytogenes* (Pfeffer et al., 1993; Rothe et al., 1993). Together, these data show that solTNF and TNFR1 are necessary for inflammation while tmTNF and TNFR1 are critical for anti-Listerial defense.

By contrast to the widely expressed TNFR1, TNFR2 expression is restricted to immune cells, endothelial cells, and several CNS cell types (see below), and fewer independent activities have been identified. TNFR2 lacks a death domain and mainly activates pro-survival signals by direct recruitment of TRAF2 and subsequent activation of PKB/Akt and NF-κB pathways (Medvedev et al., 1994; Rao et al., 1995). These properties, coupled with its activation by both tmTNF and solTNF (Grell et al., 1995), and the finding that TNFR2-deficient mice have increased levels of serum solTNF in response to lipopolysaccharide (LPS) injection and exacerbated TNFR1-mediated inflammation (Erickson et al., 1994; Peschon et al., 1998), suggest it is more likely to play a role in specific local homeostatic processes and possibly the reinforcement of TNFR1-mediated responses, although it is likely that further unique functions for this receptor will be discovered.

EARLY STUDIES OF TNF IN THE CNS

In general, TNF plays a prominent role in the induction and maintenance of inflammation including that in the CNS (Fig. 1). Elevated production of TNF is evident in patients and animal models of a wide range of CNS pathologies including chronic diseases such as MS (Hofman et al., 1989; Sharief and Hentges, 1991; Selmaj et al., 1991a), Alzheimer's disease (AD) (Fillit et al., 1991; Paganelli et al., 2002), Parkinson's disease (PD) (Boka et al., 1994; Mogi et al., 1994, 2000), HIV encephalopathy (Grimaldi et al., 1991) and meningitis (Leist et al., 1988) as well as following acute injuries such as cerebral stroke (Liu et al., 1994; Barone et al., 1997) and trauma (Ross et al., 1994; Gourin and Shackford, 1997). In the mouse, circulating TNF has been shown to cross the BBB into the brain via a specific saturable transport system (Gutierrez et al., 1993). TNF is also produced constitutively in the CNS by several populations of neurons (Breder et al., 1993). Inflammatory stimuli such as LPS and cytokines induce TNF production by additional CNS cell types, particularly microglia which are a rich source of TNF (Sawada et al., 1989), astrocytes (Lieberman et al., 1989; Chung and Benveniste, 1990) and ependymal cells of the choroid plexus (Tarlow et al., 1993). Under conditions of pathology, such as experimental cerebral ischemia, TNF is also expressed by injured neurons and infiltrating immune cells (Liu et al., 1994; Botchkina et al., 1997).

There is a large body of evidence that TNF is a key mediator of secondary CNS damage following acute

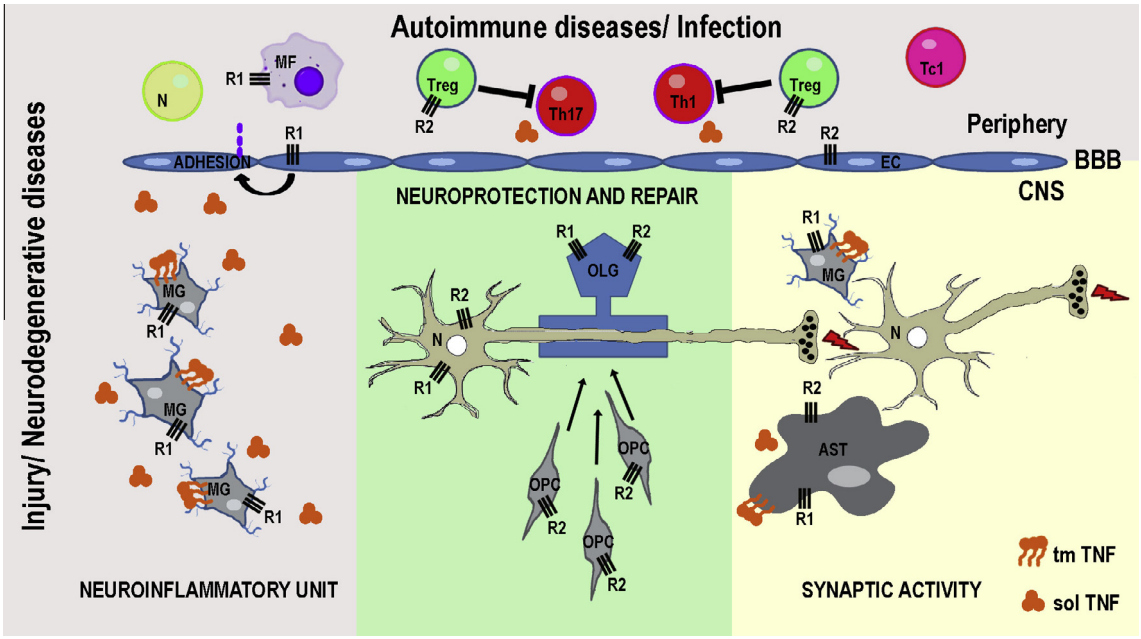

Fig. 1. Diagrammatic representation of the main cellular sources, molecular forms and receptor targets of TNF in the CNS under physiological and pathological conditions. Under physiological conditions (yellow) and during host defense responses (green), TNF expression is induced by basal activity in microglia (MG), neurons (N) and astrocytes (AST) and is important for regulating neuronal function, including synaptic activity. Neurons also constitutively express TNFR1 and TNFR2, which are important for mediating neuroprotection against neurotoxic stimuli, while oligodendrocytes (OLG) and OPC express TNFR2, which is necessary for OPC proliferation and myelin repair. Under conditions of autoimmunity or chronic neurodegeneration (pink), the primary disease trigger activates microglia to chronically produce high levels of solTNF, resulting in a local "neuroinflammatory unit" and secondary tissue damage together with infiltration of CNS tissues by peripheral immune cells such as macrophages (MF), neutrophils (N) as well as CD4 + (Th1, Th17) and CD8 + (Tc1) lymphocytes following the upregulation of adhesion molecules such as VCAM and ICAM by endothelial cells (EC).

injury and under conditions of chronic inflammation. Intracerebral administration of TNF 24 h before the induction of transient or permanent experimental ischemia exacerbated neurological defects and lesion size, and these effects were reversed by co-administration of a neutralizing anti-TNF antibody (Barone et al., 1997). TNF induces leukocyte adhesion to cerebral vessels through the upregulation of adhesion molecules such as VCAM and ICAM (Pober and Cotran, 1990) and can contribute to blood–brain barrier (BBB) disruption (de Vries et al., 1996). Soluble human TNF, which signals efficiently through mouse TNFR1, not TNFR2 (Lewis et al., 1991), also induced delayed-onset oligodendrocyte necrosis and dilation of myelin when administered to myelinated cultures of mouse spinal cord tissue (Selmaj and Raine, 1988), indicating a cytotoxic effect of TNF/TNFR1 signaling on oligodendrocytes that has direct implications for the pathogenesis of demyelinating diseases. Consistent with this, transgenic mice that overexpress human or mouse TNF transgenes from CNS glia induced oligodendrocyte apoptosis, neuroinflammation and the development of demyelinating lesions similar to those seen in MS (Probert et al., 1995; Akassoglou et al., 1997, 1998) and enhanced severity of EAE, an animal model for MS induced by immunization with myelin auto-antigens (Taupin et al., 1997). Local CNS production of TNF was responsible for the exacerbated EAE pathology seen in mice deficient in cytokine ciliary neurotrophic factor (CNTF), a survival factor for neurons and oligodendrocytes, because disease increase was prevented by treatment with anti-TNF antibody (Linker et al., 2002).

Genetic studies in mice confirmed the importance of TNF in the induction phase of EAE and revealed critical points of TNF action during disease progression that were generally consistent across the different strains of mice and EAE models used (Table 1). One set of studies showed that the onset of EAE is delayed in TNFKO mice, which are deficient in both solTNF and tmTNF, and this was associated with altered movement of inflammatory leukocytes in the CNS, effects consistent with a pro-inflammatory, disease-advancing role for TNF. However, mice eventually developed the full-blown disease (Korner et al., 1997b; Liu et al., 1998; Kassiotis et al., 1999). Importantly, another set of studies showed that clinical symptoms and pathology, once established, became more severe in mice deficient in solTNF, tmTNF and lymphotoxin α (Frei et al., 1997), solTNF and tmTNF (Liu et al., 1998) or TNFR1 (Kassiotis and Kollias, 2001). TNFKO also converted mice of the 129/SV strain from EAE-resistance to susceptibility and the i.v. administration of human TNF abrogated disease in TNFKO mice (Liu et al., 1998). Collectively, these data were among the first to hint that TNF exerts differential roles at different stages of autoimmune demyelination, with solTNF, and not tmTNF, advancing inflammation and the onset of new disease, while solTNF and/or tmTNF were protective in established disease by limiting the extent and severity of autoimmune pathology.

Consistent with the inflammatory effects of TNF, the peripheral or central administration of anti-TNF antibodies or soluble TNF receptors ameliorated disease in a variety of experimental models involving CNS inflammation including EAE induced by T cell transfer (Ruddle et al., 1990; Selmaj et al., 1991b, 1995) or active immunization (Baker et al., 1994; Korner et al., 1995, 1997a; Martin et al., 1995), cerebral ischemia (Meistrell et al., 1997; Nawashiro et al., 1997; Lavine et al., 1998) and head trauma (Shohami et al., 1996). The failure of clinical trials in MS patients using non-selective TNF inhibitors was therefore difficult to explain at the time. In one study, two rapidly progressing MS patients were treated with i.v. infusion of a humanized mouse monoclonal anti-TNF antibody in a phase I safety trial. Treatment was associated with increased disease activity as measured by increased gadolinium-enhancing MRI lesions and cell and immunoglobulin content in the CSF (van Oosten et al., 1996). In a second study, MS patients, mostly with relapsing-remitting MS (RRMS), were treated with lenercept, a dimeric TNFR1 extracellular domain fused to a human IgG1 heavy chain fragment that binds to both solTNF and tmTNF and inhibits binding to TNFR, in a phase II placebo-controlled trial. This trial was halted following an increase in the number of treated patients experiencing disease exacerbations compared to placebo and a tendency toward more severe neurological defects (Multiple Sclerosis Study Group, 1999). These trials provided strong clinical evidence that non-selective inhibition of TNF is not only non-beneficial, but positively deleterious in MS and that TNF, further to its potent pro-inflammatory role, mediates essential protective functions in the CNS. Since then, the use of non-selective TNF inhibitors for diseases such as rheumatoid arthritis and Crohn's disease has been associated with cases of new onset or exacerbation of CNS demyelinating disorders, as described on the safety warning labels of the approved TNF inhibitors, etanercept, infliximab, golimumab, adalimumab and certolizumab, and some of these cases are associated with changes in mental status or permanent neurological disability (Stubgen, 2008; Bosch et al., 2011). Collectively, these early experimental and clinical data clearly showed that, unlike in the periphery, TNF and its receptors perform both pro-inflammatory effects that exacerbate neuroinflammation and secondary neuronal damage and protective effects in the CNS under conditions of pathophysiology.

FIRST EVIDENCE FOR PROTECTIVE EFFECTS OF TNF IN THE CNS

Several independent lines of evidence showing beneficial functions of TNF in the CNS response to injury emerged alongside the studies that showed its neuroinflammatory effects.

First, brief periods of mild ischemia and hypothermia (Kirino et al., 1991; Kitagawa et al., 1991), or a single intravenous injection of LPS (Tasaki et al., 1997), induce robust tolerance against subsequent severe ischemia, a phenomenon known as ischemia preconditioning. The observation that intravenous administration of a TNF binding protein (a recombinant type I soluble TNF receptor dimer conjugated to polyethylene glycol), completely nullified the preconditioning effect of systemically-administered

LPS (Tasaki et al., 1997), showed that TNF, either or both solTNF and tmTNF, was essential for the induction of ischemia preconditioning. The further finding that pretreatment of mice by intracisternal administration of TNF preconditioned them to tolerate an otherwise damaging ischemic insult (Nawashiro et al., 1997), showed that solTNF is sufficient for initiating preconditioning tolerance through local mechanisms in the CNS.

Second, in a model of cuprizone-induced demyelination and remyelination, TNF-deficient mice showed delayed remyelination and a reduction in proliferating $NG2^+$ cells, which mainly represent oligodendrocyte precursor cells, suggesting that TNF plays an important role in the spontaneous remyelination of demyelinated axons in this model (Arnett et al., 2001). In the same study, further analysis in mice deficient in TNF receptors revealed a role for TNFR2, and therefore tmTNF, in promoting the proliferation of oligodendrocyte progenitors and in remyelination (Fig. 1).

Third, seminal studies by Mark Mattson and his team to investigate the cellular basis of neuroprotection under conditions that prevail during CNS degeneration demonstrated that TNF is not directly toxic to primary embryonic neurons. On the contrary, TNF pre-treatment strongly protected hippocampal, septal and cortical neurons against a variety of injurious stimuli including glucose deprivation, glutamate excitotoxicity (Cheng et al., 1994) and iron and amyloid-β peptide (Barger et al., 1995). TNF-induced neuroprotection correlated with attenuated elevation of stimulus-induced intracellular Ca^{2+}, was mimicked by the induction of NF-κB activity and was associated with increased expression of the calcium-binding protein calbindin-D28 k (Cheng et al., 1994; Barger et al., 1995) and the protective antioxidant enzyme MnSOD (Bruce et al., 1996). Interestingly, lymphotoxin-α (TNF-β), which also signals through TNFR1 and TNFR2, induced similar neuroprotective effects as TNF, further supporting a direct role for neuronal TNFR in signaling protection. The *in vivo* relevance of this mechanism was demonstrated in mice lacking both TNFR1 and TNFR2, which showed exacerbated neuronal damage induced by focal cerebral ischemia and kainic acid-induced epileptic seizures compared to wild-type controls (Bruce et al., 1996). Elegant studies by Bente Finsen's team using bone marrow chimeric mice later showed that brain TNF production, rather than immune cell TNF production, is responsible for neuroprotection following ischemia (Lambertsen et al., 2009).

Given that TNF has the potential to mediate multiple effects in the CNS in the context of a chronic neurodegenerative disease ranging from glial cell and stem cell activation and proliferation, vascular changes, cell death, neuron survival and beneficial effects on myelin, it is not surprising that the final outcome of non-selective TNF administration or blockade can give apparently contrasting effects across different diseases and between experimental models and human disease. Below, evidence for the functions and effects of TNF and TNFR in the CNS are reviewed in the context of knowledge of known cellular and molecular mechanisms of TNF-TNFR signaling with the aim of reconciling available "contradictory" data and gaining an integrated overall view to help assess whether or not TNF can be safely targeted for the treatment of CNS diseases.

TNF NEUROREGULATION IN THE NORMAL CNS

Several lines of evidence show that TNF plays an important role in controlling excitatory transmission in the CNS under physiological conditions (Fig. 1). TNF is constitutively expressed at low levels in the normal adult brain (Breder et al., 1993; Vitkovic et al., 2000; Boulanger, 2009). Seminal studies by Robert Malenka and his team showed that TNF is important for homeostatic synaptic scaling, a form of synaptic plasticity that allows the adjustment of the strength of all synapses on a neuron in response to prolonged changes in the cells electrical activity (Stellwagen and Malenka, 2006; Turrigiano, 2008). This process is induced by exogenously administered solTNF in cultured hippocampal neurons and is dependent on endogenous glia-derived solTNF in the hippocampus (Stellwagen and Malenka, 2006) and cortex, where it plays a specific role in experience-dependent plasticity in the developing visual cortex (Kaneko et al., 2008). TNF strengthens glutamatergic synaptic transmission by inducing a rapid (10 min) increase in surface AMPA receptor (α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid receptors, AMPAR) subunits on hippocampal (Beattie et al., 2002; Ogoshi et al., 2005; Stellwagen et al., 2005) and cortical (He et al., 2012) neurons. The constitutive presence of solTNF may even be essential for maintaining synaptic function because TNF blockade reduced surface AMPAR levels in cortical (He et al., 2012), hippocampal (Ogoshi et al., 2005; Stellwagen et al., 2005) and motor (Ferguson et al., 2008) neurons and decreased synaptic strength at hippocampal synapses (Beattie et al., 2002). Conversely, solTNF treatment reduced surface GABA receptors on hippocampal neurons (Stellwagen et al., 2005; Leonoudakis et al., 2008; Pribiag and Stellwagen, 2013) and TNF reduced AMPAR in inhibitory striatal neurons through the preferential removal of Ca^{2+}-permeable AMPAR (Lewitus et al., 2014). The net effect of such changes was increased excitatory over inhibitory synaptic transmission in hippocampal slices (Stellwagen et al., 2005) and possibly other neuronal circuits.

TNF can also potentiate excitatory transmission by coordinating glutamate release from astrocytes in a process called gliotransmission. Astrocytes and microglia are integral components of CNS synapses where they are known to be important for sensing and removing glutamate from the synaptic cleft, thereby limiting the duration of synaptic excitation (Perea et al., 2009). However, a recent study using TNF knockout mice revealed that the constitutively present TNF in control animals is critical for controlling glutamate release from astrocytes in response to elevations of intracellular Ca^{2+}, a process that potentiates excitatory synapses in the dentate gyrus of the hippocampus through the activation of presynaptic NMDAR (Santello et al., 2011). Exogenous administration of low picomolar amounts of

solTNF was sufficient to restore gliotransmission in TNF-deficient astrocytes (Santello et al., 2011). Taken together, these findings indicate that local production of solTNF at excitatory synapses in the CNS under physiological conditions is desirable for rapid neuroregulatory effects that result in strengthening of synaptic connectivity and neuronal networks under physiological conditions (Table 2).

THE MULTIPLICITY OF TNFR1 FUNCTION IN THE CNS; INFLAMMATION AND CELL SURVIVAL VERSUS APOPTOSIS VERSUS NECRO(PTO)SIS

TNF signaling through TNFR1, which is expressed on most cell types, mainly results in the activation of transcription factors NF-κB and AP-1 and the expression of genes encoding cytokines, chemokines, anti-apoptotic and cell survival molecules (Wajant et al., 2003). TNFR1 therefore plays a dominant role in mediating the cell activation and pro-inflammatory effects of TNF (Table 2). Indeed, EAE experiments in TNFR1KO mice showed complete resistance to disease (Suvannavejh et al., 2000; Kassiotis and Kollias, 2001) or a delayed onset and overall milder but progressive form of disease compared to wild-type controls (Eugster et al., 1999; Wheeler et al., 2006). Interestingly, resistance was associated either with reduced (Suvannavejh et al., 2000; Kassiotis and Kollias, 2001) or increased antigen-specific T cell priming responses, and the accumulation of inflammatory cells in CNS tissues in the chronic phase of disease (Eugster et al., 1999), including $CD4^+$IFN-γ-producing T cells (Wheeler et al., 2006). Unlike TNFKO mice, which also showed a mild, progressive form of EAE that was associated with a failed regression of T cell responses to antigen, TNFR1KO mice showed timely regression of antigen-specific T cell responses suggesting that TNF/TNFR2 signaling might be regulating chronicity of the autoimmune component (Kassiotis and Kollias, 2001), possibly through induction of regulatory T

Table 2. The main described effects of TNF and its receptors in the CNS under physiological and pathophysiological conditions

Effects induced	Ligand/receptors involved	References
Deleterious		
Pro-inflammatory effects that induce and further promote acute injury, autoimmune, inflammatory and neurodegenerative diseases of the CNS	solTNF, TNFRI	Probert et al. (1995), Shohami et al. (1996),Korner et al. (1997a,b), Taupin et al. (1997), Meistrell et al. (1997), Barone et al. (1997), Nawashiro et al. (1997), Akassoglou et al. (1998), Eugster et al. (1999), Kassiotis et al. (1999), Liu et al. (1998), Suvannavejh et al. (2000), Kassiotis and Kollias (2001), Sriram et al. (2002), He et al. (2007), McAlpine et al. (2009), Hsiao et al. (2014), Barnum et al. (2014)
Death of dopaminergic neurons *in vitro* and *in vivo*, retinal ganglion cells *in vivo*	solTNF, TNFRI	Fontaine et al. (2002), McCoy et al. (2006)
Delayed death of oligodendrocytes *in vitro* and *in vivo*	solTNF, TNFRI	Selmaj and Raine (1988)
Essential		
Protection against MS in patients (non-selective TNF inhibitors exacerbate existing and induce new human disease).	solTNF and/or tmTNF	van Oosten et al. (1996), Multiple Sclerosis Study Group (1999)
Protection against neuroinflammation, demyelination and neurodegeneration in mice (EAE)	tmTNF, TNFRI, TNFRII	Liu et al. (1998), Eugster et al. (1999), Kassiotis and Kollias (2001), Taoufik et al. (2011), Brambilla et al. (2011)
Protection of neurons against excitotoxic, metabolic and oxidative insults *in vitro*	solTNF pretreatment, tmTNF, TNFRI, TNFRII	Cheng et al. (1994), Barger et al. (1995), Mattson et al. (1997)), Shen et al. (1997)), Marchetti et al. (2004), Sriram et al. (2006), Taoufik et al. (2011)
Wild-type TNFRI protective against MS in patients(*TNFRSF1* variants, including one lacking TNFRI intracellular domains, are MS risk factors)	TNFRI	De Jager et al. (2009), Sawcer et al. (2011), Gregory et al. (2012)
TNFRI presence limits neuronal damage and increases survival in acute injury models (ischemia, temporal epilepsy)	TNFRI	Bruce et al. (1996), Gary et al. (1998), Taoufik et al. (2007), Lambertsen et al. (2009)
Preconditioning tolerance against ischemia in mice	solTNF and/or tmTNF	Tasaki et al. (1997), Nawashiro et al. (1997)
Desirable		
Synaptic scaling: glia-derived TNF potentiates excitatory glutamatergic signaling by increasing neuronal surface AMPA receptors (GluR1) and reducing $GABA_A$ receptors	solTNF	Beattie et al. (2002), Yu et al. (2002), Ogoshi et al. (2005), Stellwagen et al. (2005), He et al. (2012)
Gliotransmission- astrocyte TNF potentiates glutamatergic signaling by coordinating astrocyte glutamate release	solTNF and/or tmTNF	Santello et al. (2011)
Proliferation of oligodendrocyte precursor cells and remyelination in cuprizone-induced demyelination	TNFRII, tmTNF	Arnett et al. (2001)

cells (Chen et al., 2007). Further, studies using bone marrow chimeric mice showed that the essential TNFR1-responsive cells for EAE induction reside in the host tissue, most likely cells within the CNS (Gimenez et al., 2006). Collectively, these data show that TNFR1 is essential for the onset of CNS autoimmune disease, through induction of a pro-inflammatory environment in the CNS, but thereafter acts to limit the levels of local inflammation possibly as an indirect consequence of neuroprotection or by directly promoting repair processes. Consistent with these results, selective targeting of TNFR1 by the prophylactic administration of an antagonistic mutant TNF (Nomura et al., 2010) or antagonistic antibody (Williams et al., 2014) delayed the onset and reduced the severity of EAE but the long-term effects on disease progression were not reported. Another natural mechanism that may regulate the deleterious effects of TNF/TNFR1 signaling during CNS neurodegeneration was identified in the wobbler mouse model of motor neuron disease. Here TNF caused upregulation of the metalloprotease-disintegrin ADAM8 in the wobbler CNS, which in turn cleaved TNFR1 and mediated neuroprotection (Bartsch et al., 2010).

TNFR1 PROTECTS CNS CELLS AGAINST APOPTOSIS

As mentioned, under certain conditions that destabilize TNFR1 complex I such as reduced anti-apoptosis signaling through NF-κB, a cytosolic complex II is formed consisting of TRADD, FADD (Fas-associated death domain) and pro-forms of caspases 8 and 10 (in humans), which signals apoptosis (Wallach et al., 1999; Micheau and Tschopp, 2003). Procaspase 8 becomes activated by oligomerization and autoproteolytic processing on this apoptotic platform; releasing active heterotetrameric caspase 8 into the cytoplasm, which triggers a caspase cascade and apoptotic cell death. The NF-κB-inducible caspase 8/10 regulator c-FLIP protein can inhibit apoptosis by competitively dimerizing with caspase 8 and inhibiting its activation and thereby acts as a molecular switch between DR-induced cell death and survival (Tschopp et al., 1998). The FADD-caspase 8 platform can also be recruited and activated following ligand engagement by other DR such as Fas and TRAIL receptors (Peter and Krammer, 2003; Wilson et al., 2009), which are expressed by various cells in the CNS including neurons and oligodendrocytes (Nitsch et al., 2000; Dorr et al., 2002; Ryan et al., 2004; Spierings et al., 2004). DR-mediated apoptosis plays an important role in controlling neuron numbers and connectivity during development as well as in neurodegenerative diseases such as MS and is covered in excellent reviews (Yuan and Yankner, 2000).

Genetic studies in models of acute brain injury have clearly shown that the physical presence of TNFR1 is essential for neuroprotection and animal survival. Mice deficient in both TNFR1 and TNFR2 (Bruce et al., 1996), or in TNFR1 (Gary et al., 1998; Taoufik et al., 2007; Lambertsen et al., 2009), showed significantly enhanced tissue damage compared to wild-type controls and TNFR2KO mice following experimental cerebral ischemia, with TNFR1KO mice also showing increased post-ischemia mortality (Taoufik et al., 2007). Also, TNFR1KO mice showed increased degeneration of CA3 hippocampal neurons compared to wild-type and TNFR2KO mice in a kainic acid model of temporal epilepsy (Gary et al., 1998). In these models neuron death is mainly mediated by excitotoxicity caused by calcium influx via voltage-dependent calcium channels and receptors for the excitatory amino acid neurotransmitter glutamate, particularly the N-methyl-D-aspartate (NMDA) receptor and kainate receptors. TNF-mediated protection of cultured cortical and hippocampal neurons and in mice against excitotoxic, metabolic and oxidative insults (Cheng et al., 1994; Barger et al., 1995), was shown to involve NF-κB activation and the transcription of gene targets including the antioxidant enzyme manganese superoxide dismutase (Mn-SOD) (Mattson et al., 1997), the calcium-binding protein calbindin (Cheng et al., 1994), glutamate receptor subunits (Furukawa and Mattson, 1998), anti-apoptotic proteins such as Bcl-2 (Mattson and Camandola, 2001) and c-FLIP (Taoufik et al., 2007), and receptors for other neuroprotective factors such as erythropoietin (Taoufik et al., 2008). As TNFR1 engagement is a major trigger of inducible NF-κB activation and the transcription of cell survival molecules, it is likely to play a major role in promoting neuronal survival through mechanisms such as the stabilization of calcium homeostasis and inhibition of caspase activation and apoptosis. Indeed, we showed that neuronal expression of the caspase 8 inhibitor c-FLIP was sufficient to protect cultured TNFR1KO cortical neurons against apoptosis induced by glucose deprivation and reduce lesion volume after experimental ischemia in mice (Taoufik et al., 2007). Also, in the EAE model, inducible NF-κB activity in neurons was essential for limiting clinical deficits and CNS damage during the chronic phase of disease (Emmanouil et al., 2009).

TNFR-mediated neuroprotection is not limited to conditions of acute ischemic injury. In a mouse model for PD, induced by peripheral injection of mitochondrial complex 1 inhibitor 1-methyl-4-phenyl-1,2,3,6-tetrahydro pyridine (MPTP), mice deficient in both TNFR, but not individual receptors, showed reduced dopamine levels before and after acute MPTP intoxication compared to controls although numbers of nigral dopaminergic neurons were not altered (Rousselet et al., 2002). In another study, acute MPTP intoxication increased neuronal damage in the hippocampus of double TNFR-deficient mice, pointing to a combined neuroprotective effect of the two TNFR (Sriram et al., 2006). In contrast to hippocampal neurons, dopaminergic neurons were protected against MPTP neurotoxicity in double TNFR-deficient, but not single TNFR-deficient mice, an effect that was associated with reduced glial cell activation (Sriram et al., 2002, 2006; Leng et al., 2005). The possibility that TNFR1 and TNFR2 promote dopamine neuron toxicity through combined effects on neuroinflammation would be consistent with growing evidence that implicates microglia and inflammatory processes in the pathophysiology of PD (McCoy et al., 2006; McCoy and Tansey, 2008; Hirsch and Hunot, 2009).

On the other side of the coin, while the majority of studies point to a direct neuroprotective role for the

TNF-TNFR1-NF-κB signaling axis in models of ischemia and trauma, in other models TNFR1 is implicated in severe neuronal loss. In a mouse model of retinal ischemia, which induces ischemia–reperfusion injury and a significant loss of neurons from all retinal cell layers by necrosis, TNFR1KO mice were completely protected. Neuron survival in this model was dependent on the activation of an Akt/phosphatidylinositol 3-kinase signaling pathway, possibly mediated by TNFR2 (Fontaine et al., 2002). In this model, it is possible that the pro-inflammatory effects of solTNF/TNFR1 signaling mask the contribution of TNF to neuroprotection, although a direct effect of TNFR1 in degeneration of retinal neurons cannot be excluded.

In oligodendrocytes, DR including TNFR1 are implicated in the direct induction of death *in vitro* and *in vivo*. Oligodendrocytes express TNFR1, TNFR2 and Fas in CNS tissues in MS and EAE (D'Souza et al., 1996; Raine et al., 1998; Brambilla et al., 2011). Mice carrying natural mutations *lpr* and *gld* express inactive forms of Fas and Fas ligand respectively and develop markedly reduced EAE in the presence of competent immune responses (Malipiero et al., 1997; Sabelko et al., 1997; Waldner et al., 1997). Reduced EAE in these mice is thought to be due to reduced oligodendrocyte death and therefore restimulation of autoreactive T cells *in vivo* by cognate antigen. Consistent with this, mice conditionally deficient in Fas (Hovelmeyer et al., 2005) or FADD (Mc Guire et al., 2010) in oligodendrocytes showed markedly reduced EAE accompanied by reduced demyelination and oligodendrocyte apoptosis indicating a direct role for Fas in the demise of oligodendrocytes and demyelination in EAE. TNF induced oligodendrocyte and myelin damage when applied to myelinated cultures of mouse spinal cord (Selmaj and Raine, 1988) and mice doubly deficient in TNFR1 and oligodendrocyte-specific Fas were resistant to EAE (Hovelmeyer et al., 2005). However, the mechanism by which TNF contributes to oligodendrocyte death remains to be established. Importantly, a series of studies by Cedric Raine and his colleagues revealed that dying oligodendrocytes show features of lysis rather than apoptosis in MS and EAE lesions (Raine et al., 1998). In fact TNF induced "non-classical" apoptotic death in cultured human oligodendrocytes that was not associated with caspase activation, not prevented by the pan caspase inhibitor zVAD-fmk, and was dependent on apoptosis inducing factor (AIF), all features consistent with DR-induced necrosis (Jurewicz et al., 2005). It remains to be determined whether and under which conditions TNF can further promote oligodendrocyte death by the induction of necroptosis (see below).

TNFR1 PROTECTS CNS CELLS AGAINST NECROSIS

The anti-apoptotic properties of TNFR1 signaling may only partially explain the neuroprotective effects of this receptor in acute CNS injuries and why they fail to protect neurons against insults such retinal ischemia–reperfusion injury and oligodendrocytes against immune-mediated damage in MS and EAE. Over the past decade detailed biochemical analyses have revealed additional complexity in TNFR1 signaling pathways and their regulation and have revealed further mechanisms that might contribute to the neuroprotective properties of this receptor. A seminal paper by Peter Brouckaert's group tested whether caspase inhibition would alleviate TNF toxicity *in vivo*. Surprisingly, pan-caspase inhibition by administration of the protease inhibitor zVAD-fmk in mice exacerbated TNF toxicity by enhancing oxidative stress and mitochondrial damage (Cauwels et al., 2003). Studies by Peter Vandenabeele and others showed that cell death triggered by TNFR1 engagement incorporates an additional switch that decides between caspase-induced apoptosis and necrosis. Detailed biochemical studies have identified the kinases receptor-interacting protein 1 (RIP1) and RIP3 as key signaling molecules in TNF-induced programed necrosis, named necroptosis, in which RIP3 is activated and induces reactive oxygen species accumulation, calcium influx and lysosome destabilization leading to energy failure and death (Zhang et al., 2009; Vandenabeele et al., 2010). The implications of these results are that TNFR1 signaling and the FADD/caspase 8 apoptotic platform represent an additional layer of protection at cellular and organism levels that allows cells to die "decently" by apoptosis, thereby avoiding inflammation induced by necroptotic cell death. Pan-caspase inhibition was first found to modify neuronal responses by Mark Mattson, who showed that zVAD-fmk increased glutamate-induced Ca^{2+} responses in cultured hippocampal neurons, an effect that was attributed to reduced proteolysis of AMPAR (Mattson, 2000). It was hypothesized that caspase-mediated cleavage of AMPAR subunits might prevent excitotoxic necrosis by switching cells to apoptotic death (Mattson, 2000). More recently, it was shown that activation of caspase 3 via mitochondria is required for the internalization of AMPAR at synapses suggesting that caspase inhibitors might also enhance neuronal sensitivity to glutamate excitotoxicity (Li et al., 2010). A specific role for necroptosis in neuronal death was revealed by recent studies, which showed that RIP3-mediated necroptosis is activated in mouse hippocampal neurons after i.c.v. administration of TNF (Liu et al., 2014) and that necrostatin1, a specific inhibitor of necroptosis, reduced neuron loss in a model of intracerebral hemorrhage (Su et al., 2015). The importance of caspase activity for neuroprotection was also revealed unexpectedly in our own studies investigating the mechanism of TNFR1 neuroprotection in a model for stroke induced by permanent middle cerebral artery occlusion (pMCAO). In this model, reduced blood supply induces acute local energy failure and a core of irreversible necrosis around the infarct (Dirnagl, 2012). The initial lesion further expands through delayed death mechanisms involving apoptosis over a period of days and cell death in this penumbra region can be limited by inducible mechanisms of neuroprotection (Dirnagl, 2012). We and others have previously reported that lesion volumes in TNFR1KO mice were similar to wildtype controls 3 and 6 h after pMCAO, but were significantly larger by 24 h, showing that TNFR1 plays an essential role in limiting infarct progression beyond the

necrotic core by inhibiting apoptosis (Gary et al., 1998; Taoufik et al., 2007). Interestingly, i.c.v. administration of the pan-caspase inhibitor, zVAD-fmk prior to pMCAO resulted in significantly larger lesions in TNFR1KO compared to controls at 6 h after pMCAO, a time point when lesion volumes are otherwise similar in the two groups (Fig. 2) (Petit and Probert, unpublished data). These results show that pan-caspase inhibition not only fails to protect mice against apoptotic cell death following pMCAO, but also reveal an essential role for TNFR1 in limiting early and massive expansion of lesion volume under conditions that favor necroptotic cell death. From the available evidence it is therefore possible that TNFR1 mediates neuroprotection in the CNS at two levels; one by gene induction and *de novo* production of survival molecules and another, in the absence of adequate survival signals, by caspase 8-dependent apoptosis, although formal proof for this remains to be established.

The reduced physical presence of TNFR1 in a cell, either by engineered deletion or by natural mutation, reduces a major pathway of cell death regulation, exposing cells to unregulated necrosis (necroptosis) by other death receptors. DR such as TNF-related apoptosis-inducing ligand (TRAIL) receptor 1 in human (TRAIL-R1, DR4), TRAIL-R2 in human and mouse (DR5) and Fas, can also trigger necrosis following ligand engagement under apoptosis-inhibitory conditions (Vanden Berghe et al., 2014). TRAIL receptors (Nitsch et al., 2000; Dorr et al., 2002; Ryan et al., 2004; Spierings et al., 2004) and low levels of Fas (Rensing-Ehl et al., 1996) are expressed by neurons, and Fas is expressed by oligodendrocytes (D'Souza et al., 1996) and can mediate ligand-induced neuronal death in response to ischemic injury (Martin-Villalba et al., 1999) and beta-amyloid toxicity (Uberti et al., 2007). These

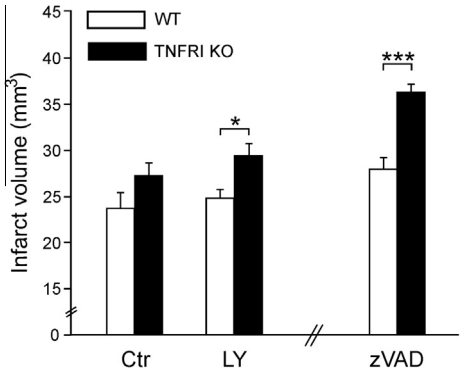

Fig. 2. Effects of inhibition of PI3 kinase and caspases upon infarct volume in wild type and TNFR1 KO mice in a model of focal ischemia. Mice were pre-treated by i.c.v. administration of the PI3 kinase inhibitor Ly294002 (320 ng/mouse) or the pan-caspase inhibitor zVAD.FMK (50 nmol/mouse), prior to permanent middle cerebral artery occlusion (pMCAO). Mice were sacrificed 6 h post-ischemia and comparison of the mean infarct volumes of each group revealed significant increases in lesion volume in TNFR1KO mice that had been pretreated with Ly294002 or zVAD.FMK. $^{*}P < 0.05$, $^{***}P < 0.001$ for pairwise comparisons between wild type and TNFR1KO mice by Student's *t* test.

receptors contribute to neurotoxicity in various conditions of neurodegeneration (Aktas et al., 2007; Haase et al., 2008), including experimental cerebral ischemia–reperfusion injury (Martin-Villalba et al., 1999) and EAE (Aktas et al., 2005). TRAIL neurotoxicity becomes particularly relevant in inflammatory and autoimmune diseases since TRAIL ligand is not expressed in the CNS but is expressed by activated T and B lymphocytes and monocytes which infiltrate CNS tissues during disease. Although TRAIL has been shown to exert immunoregulatory effects in the periphery, intracerebral administration of a soluble TRAIL-neutralizing receptor protected mice against the clinical symptoms of EAE and immune-mediated damage to neurons and myelin without alteration of antigen-specific immune responses in the periphery and CNS (Aktas et al., 2005). Taken together, these data show that DR of the TNFR superfamily contribute to the death of neurons and other CNS cells under conditions of neurodegeneration, and their pro-apoptotic effects are likely to be regulated by TNFR1-induced inhibitors of caspase 8 such as cFLIP, cIAPs etc. It can be envisioned that DR would trigger elevated levels of apoptosis and necroptosis under conditions where TNFR1 function and its anti-apoptotic signaling is reduced or absent.

Clinical data supporting a role for diminished TNFR1 signaling in the pathogenesis of MS has come from genetic studies in humans. Genome-wide association scans for MS susceptibility in large patient cohorts firmly identified a variant in *TNFRSF1A*, the gene encoding TNFR1, as a risk factor for MS (De Jager et al., 2009; Sawcer et al., 2011), but not other autoimmune conditions including rheumatoid arthritis (Stahl et al., 2010), psoriasis (Strange et al., 2010) and Crohn's disease (Franke et al., 2010), and as a protection factor for ankylosing spondylitis (Cortes et al., 2013). Two independent MS susceptibility alleles were identified in this locus: rs1800693 located proximal to the exon6/intron 6 boundary which results in a risk "G" allele and skipping of exon 6, and rs414584, located in exon 4, which is associated with an arginine to glutamine substitution at position 92 (R92Q) (De Jager et al., 2009). Functional studies showed that the rs1800693 variant encodes a truncated, soluble form of TNFR1 that lacks the transmembrane and cytoplasmic domains necessary for the proper subcellular localization and signaling of TNFR1 and to associate with full-length TNFR1 to form receptor heterotrimers with modified properties (Gregory et al., 2012). This soluble receptor could still bind to and neutralize the TNF ligand (Gregory et al., 2012). Importantly, as noted by these authors, this finding parallels the clinical experience with non-selective TNF inhibitors in MS patients, where exacerbated disease was observed, and thereby establishes a causal relationship between diminished TNF signaling and MS pathogenesis. Based on current knowledge, the TNFR1 variant could contribute to MS by encoding a new natural TNF antagonist as well as by reducing TNFR1 intracellular signaling, which, as described above, is important for inducing protection mechanisms in stressed cells such as neurons.

ROLE OF TNFR2 IN NEUROPROTECTION AND REPAIR

The expression of TNFR2 is highly regulated and found in few cell types; immune cells particularly regulatory T cells (Chen et al., 2008), endothelial cells, oligodendrocyte lineage cells (Tchelingerian et al., 1995) and some populations of neurons (Fig. 1); typically cells that rapidly increase energy demands during immune responses or cytoprotection against acute stress stimuli. TNFR2 is a non-DD-containing receptor; it responds to tmTNF and solTNF engagement and induces pro-survival signaling pathways through the direct recruitment of TRAF2 (Rothe et al., 1995) and activation of the phosphoinositide-3OH kinase (PI3K) and NF-κB pathways (Medvedev et al., 1994; Rao et al., 1995). It is involved in cell proliferation processes (Tartaglia et al., 1993; Grell et al., 1998) and also potentiates the effects of TNFR1 in inducing both cell survival and cell death (Medvedev et al., 1994; Weiss et al., 1997). Functions of TNFR2 in the CNS were revealed using experimental models (Table 1). EAE experiments in TNFR2KO mice showed increased disease severity compared to controls (Eugster et al., 1999), possibly a result of elevated levels of circulating solTNF reported in these mice (Erickson et al., 1994), as well as the absence of important neuroprotection and repair processes (see below). Seminal studies by the teams of Ulrich Eisel and Klaus Pfizenmaier show that TNFR2 plays an important role in neuroprotection against acute excitotoxic and ischemic injuries. In a model of retinal ischemia–reperfusion injury, TNFR2KO mice showed increased neurodegeneration while TNFR1KO showed reduced neuron loss. Neuroprotection in TNFR1KO mice was associated with activated Akt/protein kinase B and inhibited by intravitreal administration of a phosphatidylinositol 3-kinse inhibitor (Fontaine et al., 2002). TNFR2KO neurons were also deficient in TNF-mediated protection against glutamate excitotoxicity, and administration of the phosphatidylinositol 3-kinase inhibitor LY294002 inhibited TNF-mediated protection in wild-type and TNFR1KO neurons (Marchetti et al., 2004). Consistent with the neuroprotective properties of TNFR2, a human TNFR2-specific agonistic TNF protected dopaminergic neuronal cells against oxidative stress in *in vitro* models for PD (Fischer et al., 2011). In an independent study, knockdown of TNFR2 with antisense nucleotides in neuronal cells increased death in response to hypoxia, amyloid-β, and TNF (Shen et al., 1997). Further evidence for a protective function of Akt/protein kinase B was found in the pMCAO model for cerebral stroke. Here, i.c.v. administration of Ly294002 prior to pMCAO resulted in significantly larger lesions in TNFR1KO compared to wildtype controls at 6 h after pMCAO, a time point when lesion volumes are otherwise similar in the two groups (Fig. 2) (Petit and Probert, unpublished data).

Together these studies show that TNFR2 signaling through PKB/Akt and long-term NF-κB activation represents an important mechanism of neuronal survival following ischemia–reperfusion injury, glutamate excitotoxicity, oxidative stress and possibly other death stimuli, via Akt/protein kinase B and NF-κB signaling pathways presumably leading to the transcription of survival and anti-apoptotic target genes. Under conditions of human tmTNF transgene overexpression in the mouse CNS, a physiologically regulated human TNFR2 transgene was further sufficient to trigger pro-inflammatory effects characterized by vascular activation and meningeal and vascular inflammation, resulting in secondary tissue damage (Akassoglou et al., 2003). Further to a direct neuroprotective effect, TNFR2 might also reinforce TNFR1-mediated cell-survival and, if necessary, apoptotic signaling, thereby maximizing neuroprotection mediated by tmTNF (see below). Positive co-operation between TNFR2 and TNFR1 has been described in cell survival, where responses that are initiated by both receptors via identical pathways through activation of NF-κB are additive, as well as in cell death where TNFR1-induced cytotoxicity is potentiated by the existing stimulation of TNFR2 (Medvedev et al., 1994; Weiss et al., 1997). Taken together, evidence indicates that the two TNF receptors might co-operate to mediate direct neuroprotective effects in the CNS.

TNFR2 mediates additional beneficial activities that would act to reduce tissue damage and enhance repair during autoimmune demyelination (Fig. 1). TNFR2 is expressed at high levels by human and murine regulatory T cells (Annunziato et al., 2002; Chen et al., 2008) and mediates their activation and expansion in mice (Chen et al., 2007), effects that might suppress CNS-directed autoimmune T cell responses (Fig. 1). Furthermore, as previously mentioned, TNF and TNFR2 both promote oligodendrocyte precursor cell proliferation and remyelination in a mouse model of cuprizone-induced demyelination and remyelination (Arnett et al., 2001). Insights into the mechanisms that underlie these effects were provided recently, by the findings that TNFR2 protects oligodendrocyte precursor cells against oxidative stress (Maier et al., 2013) and that astrocyte TNFR2 mediates oligodendrocyte precursor cell proliferation and differentiation via CXCL12 (Patel et al., 2012) and oligodendrocyte maturation via secretion of leukemia inhibitory factor (Fischer et al., 2014). Together these effects might contribute to the maintenance of myelin sheaths, not only after their damage but also under physiological conditions (Fig. 1).

SOLUBLE TNF

It is already obvious that solTNF, which mediates the pro-inflammatory effects of TNF via TNFR1 signaling, and the ligand-binding domains of TNFR1 itself, represent major therapeutic targets for the treatment of chronic inflammatory diseases (see also review by Fischer et al., 2015). Investigation into the differential roles of solTNF and tmTNF in the CNS was first made possible by the development of tmTNF knockin mice in which the endogenous TNF gene was replaced by a mutant TNF gene that encodes uncleavable tmTNF (Table 1). In these mice the initiation of autoimmune pathologies, including EAE, is severely compromised demonstrating the dominant role of solTNF, and therefore also TNFR1, in the

pathogenesis of inflammation (Ruuls et al., 2001; Alexopoulou et al., 2006). The development of selective inhibitors of solTNF and of TNFR1 therefore opened up an entirely new chapter in the investigation of TNF function, circumventing the need for permanent gene deletion or mutation in the germ-line of mice and possible compensatory effects by other genes and pathways, and allowing the therapeutic value of selective solTNF/TNFR1 inhibition over non-selective TNF inhibition, to be assessed in the pre-clinical animal models.

Dominant negative TNF mutants (DN-TNFs) represent a novel class of anti-TNF biologics that selectively inhibit solTNF while preserving the effects of tmTNF (Steed et al., 2003; Zalevsky et al., 2007). DN-TNFs are engineered variants of human solTNF that form heterotrimers with endogenous (human and murine) solTNF and thereby prevent solTNF binding to TNFR1. Importantly, DN-TNFs ameliorate peripheral inflammation as efficiently as the non-selective TNF inhibitor etanercept, and unlike etanercept preserve host defense responses to *Listeria monocytogenes* (Steed et al., 2003; Zalevsky et al., 2007). As expected, DN-TNFs recapitulated the results obtained in tmTNF knockin mice. The effects of systemic or direct CNS administration of DN-TNFs has now been investigated under diverse experimental neuroinflammatory conditions and revealed a surprisingly wide range of beneficial effects, as well as having the advantage of being able to penetrate the BBB at pharmacologically-relevant levels in normal mice (Karamita, Tansey & Probert, unpublished results). Further, in diseases such as EAE and focal cerebral ischemia, where BBB function is disrupted, the comparison of selective inhibition of solTNF using DN-TNFs with those of non-selective TNF inhibition using etanercept, an IgG1 Fc-TNFR2 fusion protein (Murray and Dahl, 1997), which does not normally penetrate the BBB, has allowed investigators to gain insights into the differential functions of sol and tmTNF in disease pathogenesis. A recently described BBB-penetrating non-selective inhibitor of human TNF, based on the extracellular domain of the TNFR2, which shows similar affinity for TNF as etanercept and provided neuroprotection in a mouse model of PD (Zhou et al., 2011), should facilitate comparative studies of solTNF and tmTNF functions in a wider range of neuroinflammatory disorders.

Several biologics that selectively target TNFR1 have been developed. R1antTNF is a TNFR1-selective antagonistic mutant TNF that reduced liver injury in a model of acute hepatitis (Shibata et al., 2008) and ameliorated EAE when administered prophylactically, an effect that was associated with suppression of antigen-specific IFN-γ- and IL-17-producing T cells (Nomura et al., 2010). Specific antagonistic anti-TNFR1 antibodies have also been developed, including a monovalent domain anti-mouse TNFR1 antibody (DMS5540) that suppresses the development of experimentally induced autoimmune arthritis (McCann et al., 2014); anti-human TNFR1 nanobodies that inhibit TNF-induced liver inflammation in humanized TNFR1 mice (Steeland et al., 2015); a humanized mouse anti-human TNFR1 antibody (ATROSAB) (Kontermann et al., 2008) that awaits pre-clinical evaluation. While such reagents are expected to compare favorably to non-selective TNF inhibitors for the treatment of peripheral inflammatory disorders, and superior for the preservation of host defense responses to infections, a limited ability to cross the BBB may limit their application to CNS inflammatory disorders. Proof-of-principle that TNFR1-specific antibodies might be relevant for the treatment of MS was provided recently in an EAE model, where administration of an anti-TNFR1 antibody in prophylactic and therapeutic protocols ameliorated disease (Williams et al., 2014).

Neuroinflammation is a hallmark of all CNS neurodegenerative diseases. In PD solTNF and solTNFR1 levels are increased in cerebrospinal fluid and tissues of patients (Boka et al., 1994; Mogi et al., 1994; Hirsch and Hunot, 2009). The cause of neuronal loss in PD is not known but non-cell autonomous mechanisms, mediated by activated glia and peripheral immune cells including CD4 and CD8 lymphocytes, are thought to be important. A positive feedback mechanism whereby chronic neuroinflammation causes oxidative damage and death of dopaminergic neurons, and neurodegeneration in turn perpetuates inflammation, is likely to underlie the pathogenesis of this disease. Studies with DN-TNFs in experimental models for PD allowed Malu Tansey and her group to clarify the somewhat inconclusive results obtained using TNFR-deficient mice (see above). They demonstrated that solTNF, and therefore TNFR1, plays a critical role in mediating the death of dopamine neurons *in vitro* and *in vivo*, an effect that was associated with potentiation of microglia activation. The intranigral delivery of a PEGylated DN-TNF protein named XENP345, or a lentivirus encoding the non-PEGylated protein, reduced neuroinflammation and loss of substantia nigra dopamine neurons in endotoxin (LPS) and neurotoxin (6-hydroxydopamine, 6-OHDA) rat models for PD (McCoy et al., 2006; McCoy and Tansey, 2008). XENP345 also attenuated dopamine neuron toxicity in mixed neuron/glia cultures induced by LPS or 6-OHDA (McCoy et al., 2006). These results demonstrate that solTNF is neurotoxic to dopamine neurons and that selective inhibition of solTNF is neuroprotective. Importantly, this group also recently showed that peripheral s.c. administration of a similar DN-TNF, XPro1595, was sufficient to attenuate neuroinflammation and dopamine neuron loss in the 6-OHDA model (Barnum et al., 2014). Although it still remains to be established whether neuroinflammation is primary or secondary to dopaminergic neuron loss in PD, these studies clearly demonstrate a pathogenic role for solTNF and the therapeutic relevance of DN-TNF biologics for treatment in PD.

In AD too, experimental and clinical evidence suggest that neuroinflammation plays a key role in disease pathogenesis (McAlpine and Tansey, 2008). Activated microglia are closely associated with amyloid plaques in AD brains and elevated levels of pro-inflammatory cytokines, including solTNF, were reported in sera (Fillit et al., 1991; Paganelli et al., 2002). On the other hand, solTNF was one of the proteins selectively reduced in the plasma of patients with mild cognitive impairment leading to AD as well as patients with established AD (Ray et al.,

2007). Although apparently conflicting, these findings clearly indicate there is a systemic dysregulation of peripheral immune responses, and of TNF production, in this disease. Experimental evidence for disease-promoting effects of neuroinflammation and solTNF/TNFR1 signaling come from studies in transgenic disease models. In the APP23 model, which expresses a disease-associated mutant human β amyloid precursor protein (APP) selectively in neurons and results in extensive amyloid β (Aβ) plaque formation (Sturchler-Pierrat et al., 1997), absence of TNFR1 signaling inhibited the pathological hallmarks of AD: microglia activation, production of β-secretase 1(BACE1), an enzyme involved in processing of APP, generation of Aβ, Aβ plaque formation, neuronal loss, and prevented associated learning and memory defects (He et al., 2007). Similar beneficial effects were seen by the Tansey lab with TNFR1 deficiency or solTNF inhibition in a triple transgenic mouse model of AD (3xTG-AD), which expresses three different disease-associated genes (Oddo et al., 2003). Here transient inhibition of solTNF prior to plaque formation by infusion of XENP345 into the hippocampus, or persistent inhibition by i.c.v. injection of a lentivirus encoding DN-TNF, prevented the acceleration of AD-like pathology by systemically administered LPS, reducing both microglial activation and accumulation of APP in the brain (McAlpine et al., 2009). Interestingly, a pilot open-label clinical trial in which AD patients received perispinal infusion of etanercept or placebo claimed that patients receiving the non-selective TNF inhibitor showed improvement of cognitive performance compared to controls indicating the therapeutic relevance of TNF inhibition in AD (Tobinick and Gross, 2008). It is not immediately clear how perispinal etanercept exerts its beneficial effects in AD since it does not penetrate the BBB. Nevertheless, the clinical results with TNF inhibitors are promising and need to be confirmed in further trials.

Neuroinflammation is also a feature of Huntington's disease (HD), which is caused by an expanded CAG repeat in exon 1 of the huntingtin gene. TNF is increased in the plasma and brain tissues of HD patients and mouse models for this disease (Bjorkqvist et al., 2008). Intracerebroventricular infusion of XPro1595 in a transgenic mouse model for HD (R6/2) reduced neurotoxicity and glial reactivity and improved motor function, with significant beneficial effects being obtained also by systemic administration of XPro1595 (Hsiao et al., 2014). The finding that XPro1595 reduced the inflammatory responses of astrocyte-enriched cultures derived from R6/2 transgenic mice and induced pluripotent stem cells from HD patients in response to LPS and cytokines suggested that the beneficial effects of solTNF inhibition in HD models are at least partially due to reduction of neuroinflammation (Hsiao et al., 2014).

TRANSMEMBRANE TNF

Information concerning the role of tmTNF in the CNS under physiological and disease conditions is currently much more limited, mainly because of the impermeability of the BBB to biologics that block tmTNF function such as antibodies and receptor constructs. Further to the genetic studies in tmTNF knockin mice already described, the comparative roles of solTNF and tmTNF have been studied in EAE using DN-TNF (Brambilla et al., 2011; Taoufik et al., 2011). In EAE, selective inhibition of solTNF with XPro1595 improved clinical outcome, showing that solTNF promotes disease, whereas non-selective inhibition of both solTNF and tmTNF with etanercept did not result in protection, indicating that tmTNF has strong beneficial effects. The therapeutic effects of DN-TNF were associated with reduced neuroinflammation, demyelination and axon damage, increased remyelination accompanied by increased numbers of $NG2^+$ oligodendrocyte precursors, perhaps due to preferential TNFR2 functioning (see above), and were dependent upon neuronal NF-κB signaling (Brambilla et al., 2011; Taoufik et al., 2011). Taken together with the findings that TNFR1 is localized in neurons, oligodendrocytes, astrocytes and macrophages/microglia, that TNFR2 is localized in mature oligodendrocytes, $NG2^+$ oligodendrocyte precursor cells, astrocytes and macrophages/microglia in EAE mice and MS patients, and that tmTNF is required for neuroprotection in astrocyte-neuron co-cultures (Papazian and Probert, unpublished data), these data support an essential role for tmTNF in the protection of neurons and myelin as well as for remyelination in demyelinating CNS diseases.

DN-TNF was also beneficial in a mouse model of focal cerebral ischemia (pMCAO). In this model of acute CNS injury, the peripheral administration of two different inhibitors, XPro1595 and etanercept, had similar effects. Both XPro1595 and etanercept improved functional outcome without altering lesion volume, reducing granulocyte infiltration into the CNS and microglia activation, indicating that solTNF, which is inhibited by both treatments, plays a dominant role in promoting harmful immune responses from the periphery in this model (Clausen et al., 2014). By contrast, in a spinal cord injury model in mice, peripheral administration of TNF inhibitors had no detectable effect on improving locomotor performance after injury, while central administration of XPro1595, but not etanercept, resulted in improved locomotor function, decreased anxiety-related behavior and reduced tissue damage. Importantly, the protective effects of inhibiting pro-inflammatory solTNF function were associated with upregulated TNFR2 expression in the spinal cord, thereby facilitating tmTNF/TNFR2-mediated neuroprotection and repair functions (Novrup et al., 2014).

FUTURE PERSPECTIVES

Compelling evidence now shows that TNF-TNFR signaling in the CNS is much more than a pathogenically relevant mechanism that underlies chronic inflammation in neurodegenerative disease. The multiplicity of TNF's effects in the CNS range between essential, desirable and deleterious (summarized in Table 2) and although there is much yet to be learned about its roles in the physiology and pathophysiology of

the CNS, knowledge that is already available provides the matrix for a model upon which new findings can be critically evaluated and safer therapeutic strategies can be rationally designed. The weight of evidence incriminates solTNF and TNFR1 signaling in mediating the deleterious pro-inflammatory effects that promote autoimmune and neurodegenerative diseases and indicates that that selective targeting of these molecules with reagents such as DN TNF and anti-TNFR1 antibodies, for therapeutic purposes, would effectively reduce pathology while respecting important contributions of tmTNF, TNFR2 and intracellular TNFR1 in host defense, neuroprotection and brain repair mechanisms. A potential caveat to such an approach in the development of therapeutic targeting approaches for CNS, would be careful consideration of the effects of solTNF, and therefore probably TNFR1, in the regulation of neuronal activity through mechanisms such as synaptic scaling and gliotransmission, although such mechanisms likely take place in the sheltered environment of the synaptic cleft in the intact brain and therefore might not be susceptible to molecular inhibitors.

Our understanding of TNF function in the brain has currently gained fresh momentum alongside advances in knowledge concerning the roles of microglia, the main cellular source of TNF in the CNS, under physiological and pathophysiological conditions. Microglia are now recognized to perform important homeostatic functions in the normal adult brain that stand in sharp contrast to conventional wisdom concerning their roles in host defense, as sensors of injury and infection and initiators of innate immune responses, as well as in triggering tissue inflammation and secondary tissue damage. The availability of improved genetic tools in mice, notably microglia-specific fluorescent reporters for use with *in vivo* 2-photon microscopy, and mice in which genes can be deleted or re-expressed selectively in microglia, has been instrumental for revealing previously unsuspected roles of microglia in synaptic pruning and the maturation of neuronal circuitry during development (Paolicelli et al., 2011; Schafer et al., 2012), and in the adult brain (Davalos et al., 2005; Nimmerjahn et al., 2005) where they directly contact neuronal synapses (Wake et al., 2009; Tremblay et al., 2010) and regulate synaptic activity plasticity, learning and memory (Li et al., 2012; Ji et al., 2013; Kyrargyri et al., 2015),. The striking parallelism between the range of ‘‘beneficial’’ and ‘‘deleterious’’ functions of microglia and of their main products, tumor necrosis factor (TNF), interleukin-1β (IL-1β) and nitric oxide (NO) in the CNS, promises that the complex network of TNF ligand/receptor signaling in the CNS will soon be reconciled at a cellular level with functions of microglia, and eventually with other cells that produce and respond to this cytokine, including astrocytes, oligodendrocyte precursor cells and neurons. Interestingly to date, microglia-derived IL-1β has been implicated in the regulation of synaptic plasticity and cognitive function in the brain under physiological conditions (Rogers et al., 2011; Kyrargyri et al., 2015) and it is probable that corresponding data for TNF will emerge. In the case of microglia and TNF, important milestones will be to define the mechanisms responsible for switching microglia from normal physiologically-important cells into chronically-activated, disease-promoting cells under conditions of CNS neurodegeneration and to determine whether blockade of activated microglia products, such as solTNF, can reverse this process and provide a treatment for chronic neurodegenerative diseases such as AD, PD and MS.

CONFLICT OF INTEREST STATEMENT

The author has no conflict of interest to disclose.

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