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Pro-inflammatory cytokine TNF-α as a neuroprotective agent in the brain

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Despite the numerous reports on the role of tumor necrosis factor-alpha (TNF-α) in the brain neuropathology, very little is known about the mechanisms by which TNF-α may mediate neuroprotection. Different hypotheses pertain to the molecular and cellular effectors triggered by the activation of TNF receptors (TNFR1 and TNFR2). They are focused on diminishing the production of nitric oxide and free radicals, alteration of excitatory amino acids neurotransmission, maintenance of neuronal calcium homeostasis and induction of neurotrophic factors synthesis. In this review all these data are summarized. Moreover, possible explanations for the inconsistent data concerning the TNF-α effect on neuron are discussed.

Key words: TNF-α, TNFR1, brain, neuroprotection, NF-κB

TNF-α AND ITS RECEPTORS IN THE BRAIN

Tumor necrosis factor-alpha (TNF-α), one of the best characterized cytokines, was originally discovered in the mouse serum during endotoxemia and recognized for its anti-tumor activity (Carswell et al. 1975). Its role in the central nervous system (CNS) was not observed until 1987, when microglia was found to produce TNF-α (Frei et al. 1987). At present it is well established that apart from the microglial cells, TNF-α can also be synthesized and released in the brain by astrocytes and some populations of neurons. There is a robust and rapid increase in TNF-α expression levels in the CNS both after acute insults and in a number of chronic neurodegenerative disorders (for review see: Allan and Rothwell 2001, Viviani et al. 2004)

TNF-α is synthesized as a 26 kDa membrane-bound polypeptide precursor that is cleaved by proteolysis to release a 17 kDa subunit. The proteolysis is mediated by TNF-α converting enzyme (TACE), a proteinase that belongs to the family of mammalian adamalysins (or ADAMs – A Desintegrins And Metalloproteinases). So far, TACE/ADAM17 is the only known ADAM to process TNF-α (Black et al. 1997, Moss et al. 1997). The role of this protease in the CNS has been reviewed (Moro et al. 2003). There are some reports indicating an involvement of TACE in neuroprotective mechanisms. In rat ischemia model Hurtado and colleagues (2001, 2002) demonstrated that TACE is upregulated after ischemic brain damage and that the increase in TACE expression contributes to a rise in TNF-α and a subsequent neuroprotective effect after excitotoxic stimuli.

Upon cleavage, the released TNF-α forms a bioactive homotrimer, which then exerts its effects in an autocrine and/or paracrine manner. The pleiotropic actions of TNF-α are mediated through two distinct cell surface receptors: TNFR1 (p55) and TNFR2 (p75) (for review see: MacEwan 2002, Wajant et al. 2003). Only TNFR1 contains a cytoplasmic death domain and may directly induce apoptosis. However, TNFR1 transduction pathway is much more complex. Briefly, binding of the TNF trimer to the extracellular domain of TNFR1 is recognized by the adaptor protein TNF receptor-associated death domain (TRADD), which recruits additional proteins: receptor-interacting protein (RIP), TNF receptor-associated factor 2 (TRAF2) and FAS-associated death domain (FADD). The latter

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two proteins recruit key enzymes that are responsible for initiating TNFR1 signaling events. For instance, caspase-8 is recruited by FADD to the TNFR1 complex and initiates a protease cascade that leads to apoptosis. On the other hand TRAF2 recruits cellular inhibitor of apoptosis protein-1 and 2 (cIAP-1 and cIAP-2), two anti-apoptosis proteins that also have ubiquitin protein ligase activity. Moreover, TRAF2 may activate a mitogen-activated protein kinase (MAPK) pathway leading to the activation of c-Jun N-terminal kinase (JNK) that phosphorylates c-Jun, increasing its transcriptional activity. Finally, the protein kinase RIP is critical to the activation of the transcription factor NF-κB. Therefore TNF-α binding to TNFR1 may result in either activation of apoptosis or transcriptional activity (Fig. 1).

The role of TNFR2 in the brain is less known. For a long time it has been suggested to be responsible for proliferative regulatory signals. However, despite the fact that TNFR2 does not directly engage the apoptotic pathway, studies with TNF-α receptor-specific neutralizing antibodies showed that stimulation of this receptor relies on the induction of endogenous, membrane-bound TNF-α, which subsequently activates TNFR1 (Grell et al. 1999). Fotin-Mleczek and colleagues (2002) reported that in cancer cell lines, TNFR2 may compete with TNFR1 for the recruitment of newly synthesized TRAF2-bound anti-apoptotic factors, thereby promoting the formation of a caspase-8-activating TNFR1 complex. However, the physiological relevance of TRAF2 depletion and TNF-α receptor crosstalk remains to be evaluated.

Both TNF-α receptors in the brain are expressed by neurons and glia (Kinouchi et al. 1991, Tchelingerian et al. 1995, Dopp et al. 1997). However, receptor distribution varies depending upon activation of either apoptosis or inflammatory regulation (Botchkina et al. 1997, Sairanen et al. 2001, Figiel and Dzwonek 2007, Lambertsen et al. 2007). Despite the fact that each TNF-α receptor mediates distinct cellular responses, there is an increasing evidence of considerable overlap of their signaling capabilities in mediating biological effects (Hsu et al. 1996, Declercq et al. 1998, Quintana et al. 2005). The differential patterns of localization of TNF-α receptors in neuronal and glial cells, their state of activation and the down-stream effectors, all are thought to play an important role in determining whether TNF-α will exert a beneficial or harmful effect on CNS.

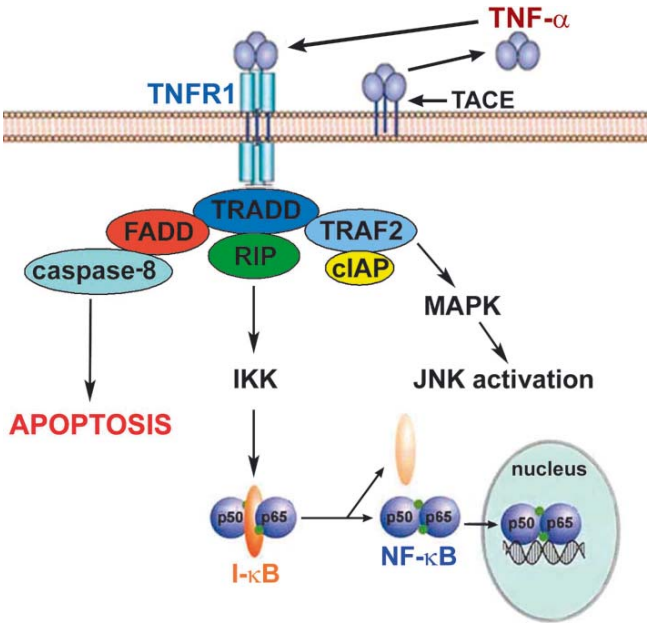

Fig. 1. An overview of TNFR1 signaling pathway. Binding of TNF-α to TNFR1 induces the recruitment of TRADD which then becomes a platform for binding of additional cytoplasmic adaptor proteins including TRAF2, RIP and FADD. The first two proteins are implicated in increasing the transcriptional activity. TRAF2 is involved in activation of JNK, a kinase that phosphorylates c-Jun. RIP is critical for activation of IKK (Ser/Thr protein kinases) that phosphorylate I-κB leading to the dissociation of the I-κB/NF-κB complex and nuclear translocation of active transcription factor. In contrast, recruitment of FADD leads to activation of caspase-8 and apoptotic machinery.

The availability of knockout mice lacking TNFR1 or TNFR2 genes has greatly facilitated research towards understanding the role of TNF-α in the brain. In 1996 Bruce and colleagues reported that mice deficient in both receptors displayed greater neuronal damage following either ischemic or kainic acid-induced excitotoxic damage (Bruce et al. 1996). Since that damage was accompanied by increased oxidative stress as well as reduced level of manganese superoxide dismutase, Mn-SOD, an antioxidant enzyme, the authors suggested that TNF-α may play a beneficial role by stimulating antioxidant pathway. In a model of nitropropionic acid (3-NP) intoxication, TNFR1/2 knockout mice exhibited increased oxidative stress and striatal lesion size (Bruce-Keller et al. 1999). Additional *in vitro* studies showed that pretreatment of neurons or astrocytes with TNF-α induced augmentation of Mn-SOD activity, and also significantly attenuated 3-NP-induced superoxide accumulation and loss

of mitochondrial transmembrane potential. Studies in mice lacking only one type of TNF-α receptor revealed that TNFR1 signaling pathway is more important then TNFR2 one in mediating neuroprotective actions of TNF-α after acute brain insults (Gary et al. 1998). TNFR1 and TNFR2 may also have opposite effect on neurons, with the former having damaging effect and the latter being neuroprotective (Fontaine et al. 2002). The exact mechanisms underlying such differential properties of TNF-α receptors have yet to be fully determined, but the dual activity of the cytokine may depend on the time and progression of the damage.

Recently TNFR2 involvement in chemical-induced apoptosis of murine hippocampal dentate granule neurons has been reported (Harry et al. 2008). In this very interesting study authors employed trimethyltin (TMT), a well known neurotoxicant, to induce neuronal injury accompanied by microglial activation and increased production of TNF-α. Using TNF receptor-deficient mice they observed exacerbation of injury that occurs in the absence of any single receptor. Moreover, they demonstrated that neuroprotection requires blocking of both receptors.

To date there is no clear consensus on the role of endogenous TNF-α in CNS acute injury. On the other hand, several reports indicate that TNF-α pretreatment may play a role in the regulation of tolerance to ischemia. It is well established that preconditioning with TNF-α affects infarct size in a time- and dose-dependent manner (Nawashiro et al. 1997). Intracerebral administration of TNFR1 antisense oligodeoxynucleotide inhibited the ischemic preconditioning-induced protective effect (Pradillo et al. 2005). In the same study lactacystin, a specific proteasome inhibitor was shown to block NF-κB activation and subsequent resistance to ischemic injury. These results clearly indicate that TNFR1 signaling pathway leading to NF-κB activation plays an important role in ischemic tolerance phenomenon. Recently, it was reported that TNF-α pretreatment up-regulated NF-κB activity and the expression of $FLIP_L$, an endogenous inhibitor of caspase-8, in primary cortical neurons after glucose deprivation-induced injury. Moreover, transgenic mice that show neuron-specific over expression of $FLIP_L$ revealed reduced lesion volume after permanent middle cerebral artery occlusion (Taoufik et al. 2007). Therefore, it is possible that $FLIP_L$ can act as a downstream mediator of TNFR1 neuroprotection.

NF-κB TRANSCRIPTION FACTOR AND NEUROPROTECTIVE ACTIONS OF TNF-α

NF-κB in the brain is typically a heterodimer that consists of p50 and p65 subunits. The activity of this transcription factor is strictly regulated. In most cells it resides in a latent, cytoplasmatically localized state, bound to inhibitory protein called I-κB that masks its nuclear localization signal. When cell receives signals that activate NF-κB, I-κB is phosphorylated at serine 32/36 and degradated by proteasomes after polyubiquitination. The degradation of I-κB frees NF-κB in the cytoplasm and allows it to translocate into the nucleus, leading to subsequent activation of target genes.

The involvement of NF-κB activation in neuroprotective effects of TNF-α has been well documented (Mattson et al. 1997, Wang et al. 1998, Sullivan et al. 1999, Tamatani et al. 1999). At least part of anti-apoptotic function of NF-κB can be explained by induction of expression of anti-apoptotic proteins (Heyninck and Beyaert 2001). These proteins include cellular inhibitor of apoptosis, cIAP. It has been reported that cIAP1 and cIAP2 can interact with TRAF2 and overexpression of cIAP1 and cIAP2 inhibits TNF-induced caspase-8 activity and apoptotic pathway (Wang et al. 1998).

Among the gene targets of NF-κB are also members of the proto-oncogene *bcl*-2 family. Treatment of primary hippocampal neurons with TNF-α prevents hypoxia and nitric oxide-induced neuronal death through NF-κB-dependent overexpression of Bcl-2 and Bcl-x (Tamatani et al. 1999).

Deregulation of cellular calcium homeostasis, resulting in a prolonged elevation of intracellular calcium levels, plays an important role in ischemic and traumatic neuronal death. Several gene targets of NF-κB in neurons encode proteins that can stabilize intracellular calcium levels, e.g. calcium-binding protein calbindin-D28k. TNF-α is beneficial in the maintenance of calcium homeostasis as it reduces the neuronal injury resulting from glucose deprivation and glutamate excitotoxicity through the up-regulation of calbindin-D28k expression in cultured hippocampal neurons (Cheng et al. 1994). Enhanced expression of calbindin-D28k was found also in TNF-α-treated astrocytes revealing increased resistance to acidotic injury and calcium ionophore toxicity (Mattson et al. 1995). Similarly, TNF-α attenuates β-amyloid-induced elevation of cal-

cium and reactive oxygen species (ROS) and this protective effect may be mediated by a pathway involving NF-κB (Barger et al. 1995). It is well established that ROS scavenger Mn-SOD promoter contains an NF-κB consensus sequence and Mn-SOD expression is increased by TNF-α (Wong and Goeddel 1988, Dopp et al. 2002).

Transcription factor NF-κB also regulates the expression of various neurotrophic factors (Friedman et al. 1996, Heese et al. 1998, Tanaka et al. 2000), proteins implicated in neuronal development, function and survival. Simultaneously, TNF-α is known to be connected with stimulation the production of neurotrophic factors. Hattori and colleagues (1993) reported that TNF-α is involved in modulating neuronal cell function through an indirect mechanism by which it stimulates the synthesis and secretion of nerve growth factor (NGF) in fibroblasts and glial cells. TNF-treated primary astrocytes revealed also up-regulation of glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) (Appel et al. 1997, Saha et al. 2006). Interestingly, TNF-α induces BDNF expression in astrocytes not only through the activation of NF-κB, but also *via* the activation of C/EBPβ transcription factor connected with ERK MAP kinase pathway (Saha et al. 2006).

It should be also emphasized that not only exogenous TNF-α, but also TNF-α released by astrocytes after stimulation with lipopolysaccharide (LPS) induces NGF and GDNF production in astrocytes (Kuno et al. 2006). These results suggest that an autocrine loop involving TNF-α contributes to the production of neurotrophic factors in response to inflammation.

Studies performed on mixed neuronal-glial cultures of hippocampal dentate gyrus exposed to TMT provided evidence that the expression of TNFR1 in astrocytes is upregulated in accordance with TMT-induced apoptosis of granule neurons and correlated with enhanced astroglial production of BDNF (Figiel and Dzwonek 2007, Figiel 2007). Therefore, it may be suggested that in response to severe neurotoxic injury the protective mechanisms employing astroglial TNFR1 are switched on.

Taken together the above data indicate that following brain injury NF-κB acts as a factor integrating signaling between glial cells and neurons and may negatively regulate apoptosis by induction of anti-apoptotic genes (Fig. 2).

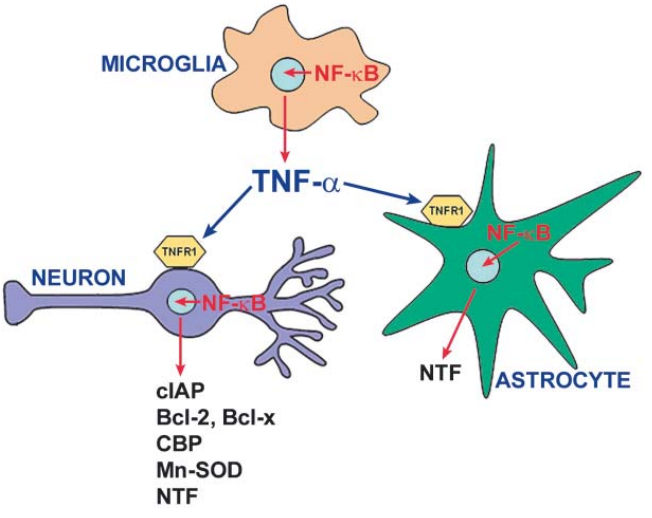

Fig. 2. Role of NF-κB in neuroprotective actions of TNF-α. Signals that activate NF-κB in microglia (e.g. ischemia, trauma, toxins) induce the production and release of TNF-α. Then TNF-α/TNFR1 interaction on neurons and astrocytes can lead to subsequent activation of NF-κB that promotes neuronal survival by inducing the expression of genes encoding anti-apoptotic proteins (cIAP, Bcl-2, Bcl-x), calcium-binding proteins (CBP), anti-oxidant enzymes (e.g. Mn-SOD) and neurotrophic factors (NTF).

TNF-α AND SYNAPTIC PLASTICITY

Several studies provide evidence that TNF-α can modulate glutamate transmission and synaptic signaling that underlies learning and memory (for review see: Pickering et al. 2005, Viviani et al. 2007). It has repeatedly been shown that NF-κB activation is also required for these phenomena.

In order to directly ascertain the involvement of endogenous TNF-α in regulation of synaptic plasticity, mice deficient in both TNF-α receptors were employed. Low frequency stimulation of Schaffer collateral axons in hippocampal slices resulted in impaired LTD (long-term depression) response in CA1 neurons. Additionally, electrophysiological measurements of synaptic transmission in slices from wild-type mice pre-incubated with κB decoy DNA also prevented induction of LTD and significantly reduced the magnitude of LTP (long-term potentiation). Since both phenomena are considered as a cellular basis for learning and memory, these interesting data indicate a critical role for TNF-α signaling pathway that modulates NF-κB activity in regulation of hippocampal synaptic plasticity (Albensi and Mattson 2000). Similarly, whole-cell perforated patch

clamp recordings in cultured rat hippocampal neurons revealed that long term treatment with TNF-α enhances calcium currents and reduces N-methyl-D-aspartate (NMDA)-induced currents by a mechanisms involving activation of NF-κB (Furukawa and Mattson 1998).

It has also been established that TNF-α acts as a modulator of excitatory amino acids' receptors trafficking. Beattie and colleagues (2002) reported that TNF-α induces an increase in cell-surface expression of AMPA receptors in cultured hippocampal neurons and influences synaptic efficacy in both primary cultures and hippocampal slices. Additionally, this study also showed that treatment with soluble form of the TNFR1, which functions as a TNF-α antagonist, had a negative effect on AMPA receptor expression and caused a clear decrease in synaptic strength. Further studies provided evidence that an exocytosis of AMPA receptor was mediated by TNFR1 and accompanied with an endocytosis of inhibitory $GABA_A$ receptors (Stellwagen et al. 2005). Since TNF-α is required continuously, it may contribute to a rapid adjustment of receptor levels at the synapse. The role of glia-derived TNF-α in homeostatic activity-dependent regulation of synaptic connectivity has been suggested (Stellwagen and Malenka 2006). On the other hand, it is well established that newly expressed AMPA receptors have lower stoichiometric amounts of GluR2 subunit, that making the receptors permeable to calcium ions (Stellwagen et al 2005). Therefore, although several data indicate that TNF-α is required for preservation of synaptic strength at excitatory synapses, enhanced calcium current through AMPA receptors containing the GluR1 subunit may lead to excitotoxic neuronal injury.

REASONS FOR DIVERGENT DATA CONCERNING THE ROLE OF TNF-α

Based on the various studies focused on the role of pro-inflammatory cytokines in the brain, TNF-α is usually regarded as agent playing an important role in sustaining and modulating neurodegenerative events or sometimes to promote cell survival (for review see: Sriram and O'Callaghan 2007, McCoy and Tansey 2008). The inconsistency of available data may be explained by the complicated molecular mechanisms utilized by TNF-α receptor-associated proteins and the complexity of the cytokine signaling system in the brain, which often involves signaling loops between one or more types of glia and neurons. It also should be emphasized that the evidence exists for regional differences in distribution and morphology of microglia, the cells that predominantly produce and release this cytokine in response to pathogenic insults. Thus, the extent of microglial activation in particular brain regions and the timing and threshold of TNF-α expression may determine its harmful or beneficial effects on neurons.

Direct evidence that different cellular composition in the targeted brain regions may reflect a differential cellular response to TNF-α exposition comes from the two ischemia models. TNF-α appears to be disease promoting in the case of retinal ischemia (Fontaine et al. 2002) while it seems to be disease ameliorating in the case of hippocampal damage (Gary et al. 1998). Similarly, the region-specific role of TNF-α was reported in MPTP-induced neurotoxicity (Sriram et al. 2006). In this study, mice deficient in TNF-α receptors showed exacerbated neuronal damage after administration of MPTP in the hippocampus, while in the striatum MPTP was unable to induce microglial activation and neuronal damage.

The differences in the TNF-α signaling, including downstream effectors such as NF-κB, may arise not only from regional specificity but also from the duration of NF-κB activity. Glutamate treatment of primary cortical neurons from TNFR1- or TNFR2-deficient mice revealed that TNFR2-induced persistent NF-κB activity is essential for neuronal survival, whereas transient NF-κB activation induced by TNFR1 is not sufficient for neuroprotection (Marchetti et al. 2004). Since different types of neurons may have different expression ratios of the two TNF-α receptors the action of this cytokine may depend on which TNF-α receptor subtype is activated.

It is well established that studies performed on *in vivo* and *in vitro* models may provide different results. It is mainly due to the lack of complete tissue organization and thereby proper cell interactions in *in vitro* conditions. Interactions between neurons and reactive microglial cells seem to be particularly important (for review see: Streit et al. 1999). Moreover, different composition of the culture may determine the results. In the majority of cases studies *in vitro* utilize cultures established from fetal rodent cerebral cortex or hippocampus, which when maintained without mitostatic agents tend to have large numbers of glia. Some studies employing these models have documented neuro-

toxicity of TNF-α. On the other hand studies performed on pure neuronal cultures reported TNF-α-induced neuroprotection. One explanation for the apparent discrepancies is that TNF-α is directly beneficial to neuronal viability, however it can evoke responses from glia that are harmful to neurons in co-culture.

To address question about mechanisms of neuron-glia interactions during CNS injury, so called "sandwich" cultures are widely used. Generally, in this *in vitro* model, separate studies of neurons and glia complement studies carried out in co-cultures, in which neurons are apposed to a glial monolayer but are separated from it by a narrow gap. Thus although the two cell types are not in contact, soluble mediators, such as pro-inflammatory cytokines, can diffuse between them. It has been reported that exposure of such "sandwich" cultures to TMT caused a higher rate of neuronal apoptosis than exposure of pure neuronal cultures. This effect was observed at TMT doses inducing significant release of TNF-α from glial cells (Viviani et al. 1998). However, in mixed cultures of hippocampal dentate gyrus, containing approximately equal number of neurons and glia, the level of microglia activation and threshold of TNF-α expression does not seem directly determine the severity of neurodegeneration (Figiel and Fiedorowicz 2002, Figiel and Dzwonek 2007). Taking into consideration that in order to prepare a "sandwich" co-culture, neurons and glial cells are in most cases derived from different brain structures in different age of the donors, the results usually differ from these obtained in mixed culture models and therefore should be interpreted with caution.

CONCLUSIONS

There is increasing agreement that pretreatment with TNF-α *in vitro* and *in vivo* may protect neurons against excitotoxic, oxidative and ischemic injuries. However, the role of endogenous TNF-α after brain injury is less clear and likely quite complex. Since TNF-α receptors are widely expressed by neurons, astrocytes and microglial cells both direct and indirect actions of TNF-α on neurons must be considered. It may be hypothesized that in many cases TNF-α is not potent to kill neurons by itself, but it may function synergistically with other cytokines and toxic agents such as NO, free radicals or glutamate. In light of the above described findings demonstrating neuroprotective actions of TNF-α, therapeutic approaches to CNS injuries based on TNF-signaling pathways in the brain should be pursued.

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