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Short Communication

Is tumor necrosis factor-α-converting enzyme (TACE) a therapeutic target for neuroprotection?

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Whether tumor necrosis factor-α (TNF-α)-converting enzyme (TACE) is a valued therapeutic target for neuroprotection is debatable given current evidence that the TNF-α/TACE mechanism may play either a protective or a destructive role in the brain in response to injury.

Inflammation has been classically defined as a physiological response of tissue whereby localized leukocyte infiltration and immune system activation lead to redness, swelling, heat and pain. Neuroinflammation refines this definition by involving the *de novo* expression of specific inflammatory mediators, such as cytokines, chemokines and adhesion molecules, which lead to the infiltration of polymorphonuclear neutrophils followed by monocytes/macrophages in response to brain injury. The neuroinflammatory reaction in the brain has been well documented in various experimental models, as well as clinical studies in both acute central nervous system (CNS) injury, including cerebral ischemia and brain trauma, and chronic CNS disease, including multiple sclerosis, Alzheimer's disease and Parkinson's disease.

TNF-α is an important immunomodulatory and proinflammatory cytokine implicated in neuroinflammation and neuronal damage that result from cerebral ischemia and brain trauma. TACE (or ADAM17) is a key sheddase that releases and activates TNF-α from its cell-bound precursor (1). Interest in targeting the TNF mechanism for neuroinflammatory diseases has been driven by recent successes with three protein-based anti-TNF biologics (etanercept, infliximab and adalimumab) in the treatment of rheumatoid arthritis, inflammatory bowel disease and psoriasis (2-4). However, drug development obstacles such as the blood-brain barrier and the high manufacturing cost of protein therapeutics make the small-molecule inhibitor approach more appropriate for the TNF/TACE mechanism in neuroprotection. A more important issue is the precise role of this mechanism in the response of the brain to injury, a concern that has been raised at both the hypothetical and experimental level, as discussed here.

It is clear that TNF-α expression is markedly elevated in various experimental models of brain injury (5-8) and that it modulates the microvascular inflammatory response. TNF-α induces neutrophil adhesion to brain capillary endothelium (9). It activates neutrophils and increases leukocyte-endothelial cell adhesion molecule expression, leukocyte adherence to blood vessels, and their subsequent infiltration into the brain (10). TNF-α disrupts the blood-brain barrier and increases capillary permeability, phenomena that are fundamental to cerebral ischemic injury. TNF-α induction of MMP-2 and MMP-9, which are also upregulated following ischemic brain injury (11, 12), is an important component of this vascular disruption. The cytokine damages myelin and oligodendrocytes (13), and increases astrocyte proliferation, which potentially contributes to demyelination and reactive gliosis. Furthermore, intracerebroventricular injection of TNF-α 24 h prior to occlusion of the middle cerebral artery exacerbates the ischemia-induced tissue injury, an effect that was reversed by ventricular administration of an anti-TNF-α monoclonal antibody (14). These data suggest that the induction of TNF-α expression after brain injury is likely to be detrimental.

On the other hand, other experimental observations have suggested protective effects. Increased TNF-α expression in the brain was observed after ischemic preconditioning, which is ischemia of short duration that confers cerebral protection to subsequent ischemic attack, and the increase was less than is typically observed after ischemic brain injury (15). Consistent with this result, intravenous pretreatment with either a low TNF-α–inducing dose of lipopolysaccharide to rats (16) or a subthreshold dose of TNF-α to mice (17) mimicked ischemic preconditioning by protecting the animals from subsequent ischemic brain injury.

Studies testing antagonists of TNF-α have also been positive in terms of neuroprotection. Pentoxifylline, a methylxanthine that reduces TNF-α production at the transcriptional level, and soluble TNF receptor 1 (TNF-R1), which acts by competing with TNF-α at the receptor, improved neurological outcome, reduced the disruption of the blood-brain barrier and protected hippocampal cells from delayed cell death following closed head injury in the rat (18). In rat focal ischemia, an anti-TNFα- monoclonal antibody and soluble TNF-R1 (repeated intracerebroventricular administration before and during focal stroke) significantly reduced infarct size (14). Likewise, topical application of soluble TNF-R1 on the brain surface significantly reduced ischemic brain injury in mice (19).

Other evidence derives from the direct targeting of TACE. A selective small-molecule TACE inhibitor, DPH-067517, significantly protected against cerebral ischemic injury (20). Unlike TNF-α, TACE is constitutively expressed in the brain and its expression is not changed in response to ischemic brain injury. Peripheral administration of DPH-067517 blocked soluble TNF-α production in ischemic brain tissue and significantly reduced both infarct size (58% decrease compared to vehicle) and neurological deficits (20). Interestingly, a similar neuroprotective effect was observed when DPH-067517 was administered 1 h after ischemic injury (20).

The detrimental role of the TNF-α/TACE mechanism remains controversial based on other lines of experimental evidence. The neuroprotective effect of TACE was demonstrated in two separate studies. Increased expression of TACE was observed in both *in vitro* (21) and *in vivo* (22) ischemic preconditioning models. Ischemic tolerance was blocked by the TACE inhibitors BB-1101 (22) and BB-3103 (23). There is also evidence for a role of TACE in neurodegeneration. TACE has been co-localized with Alzheimer's amyloid precursor protein (APP) in the amyloid plaques of the brain (24). TACE cleaves APP between residues 16 and 17 of the β-amyloid (Aβ) domain and thus may have an antagonistic role in amyloidogenesis by preventing the generation of Aβ, whereas the cleavage of APP by β-secretase (BACE) and γ-secretase in neurons results in the production of Aβ (25).

Genetic models provide another method of evaluating the TNF-α mechanism, but again the results are inconclusive. Mice deficient in TNF-α were protected from ischemic brain injury, with a 65% reduction in infarct size, and showed reduced mortality and reduced recruitment of inflammatory cells following focal stroke when compared to wild-type littermates (26). Likewise, deficits in memory retention and neurological motor function were significantly less in TNF-α-deficient mice compared to wild-type mice in a controlled cortical impact brain injury model (27). In contrast, mice deficient in TNF-R1 had an increased infarct size following transient occlusion of the middle cerebral artery, and those deficient in TNF-R2 showed similar ischemic brain injury compared to wild-type mice (28), suggesting a neuroprotective or neutral role for TNF-α in ischemic brain injury.

Experimental studies to date have led to the conclusion that the TNF-α/TACE mechanism has the potential to play both detrimental and neuroprotective roles in CNS injury. Similar disparities in outcome have also been demonstrated with other inflammatory mediators (such as IL-1) in acute brain injury (29, 30). Furthermore, a number of endogenous antiinflammatory systems, such as IL-1 antagonist, IL-10 and transforming growth factor-β (TGF-β), are thought to be concomitantly upregulated to protect the brain from injury (31-34). Both the TNF mechanism and the process of neuroinflammation itself may prove to be detrimental, beneficial, or both, as cerebral tissue adapts to maintain homeostasis following injury. Nevertheless, to the extent that neuroinflammation is not a feature of healthy brain tissue, the anti-TNF-α/TACE approach, or a general antiinflammatory approach, remains an attractive option for the treatment of acute ischemic or traumatic brain injury.

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