Antagonistic function of TNF receptors in neurodegeneration

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Tumor necrosis factor (TNF) is upregulated in a great number of neurodegenerative diseases like stroke, Alzheimers disease Multiple Sclerosis or Parkinsons disease. We have investigated the functional role of TNF and its receptors in various disease models in vivo (Fontaine et al., 2002) and in vitro (Marchetti et al., 2004). In our studies we found that, besides the pro-apoptotic signaling capacity of TNF receptor 1, TNF receptor 2 has a strong neuroprotective effect both in retinal ischemia and in excitotoxic stress in primary cortical neurons. Primary cortical neurons from transgenic mice expressing TNF are almost completely resistant against glutamate induced cell death. This effect can be mimicked by pretreatment of wild-type neurons and neurons from TNFR1 deficient mice. However, neurons from TNFR2 deficient are sensitive against TNF induced apoptosis and are not protected against glutamate. Upon stimulation with glutamate and TNF wild-type neurons and TNFR1 deficient neurons show an increased in a phopho-inositol 3 kinase (PI3K) dependend PKB/Akt phosphorylation and NF-κB activation. Inhibition of both PI3K and NF-κB leads to a reversion of the protective phenotype. In addition, we could observe a co-operation between TNFr2 and the NMDA receptor in the activation of PKB/Akt and NF-κB. Future investigations are aimed to find out how the PI3K/Akt dependend pathway is linked to TNFR2 and how the NMDAR and TNFR2 are co-operating. To investigate the potential usefulness of the TNFR2 induced signaling pathway in a therapeutic strategy of Alzheimers disease we will in future investigate the role of TNF in Aβ induced cell death *in vitro* and in transgenic mice carrying the Swedish and London mutation of the human amyloid precursor protein (APP^{SL}) and the presenilin 1 mutation (PS1) *in vivo*.

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