
Inflammatory Marker of Cognitive Decline

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Which marker tell us what at which point of the pathogenesis of cognitive impairment, MCI, AD?

The functions of the markers vary with the progression of the illness

Inflammatory markers excreted close to SP promote A β deposition

- acute phase proteins (e.g., α 1-chymotrypsin, CRP)
- chemokines such as the monocyte chemoattractant protein-1 and IP-10, ACT
- chemokine receptors (CXCR2, CCR3 and CCR5)
- key enzymes of inflammation such as nitric oxide synthase (NOS) and cyclooxygenase (COX)
- inflammatory cytokines
- sICAM-1, sVCAM-1, albumin

The Vicious Cycle

- Cytokines or chemokines up-regulation promote the production and deposition of A β
 - A β seem to induce the production of various inflammatory cytokines and chemokines in astrocytes, microglia, and in some cases, neurons, which sets off a vicious cycle whereby A β production stimulates cytokine synthesis and cytokines, in turn, stimulate A β synthesis and amyloid formation
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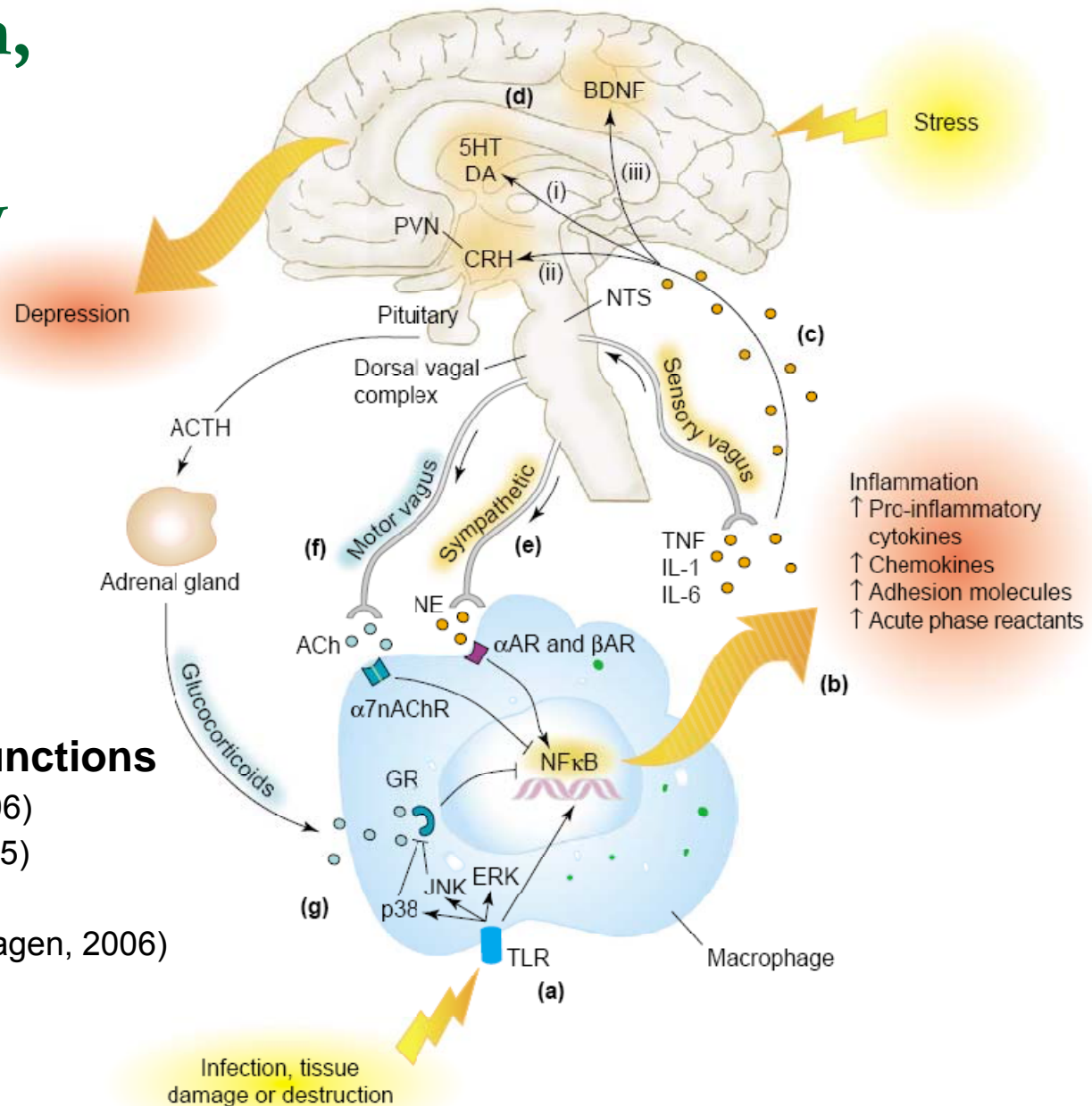
The Measure of A β 42 and A β 40 in Plasma

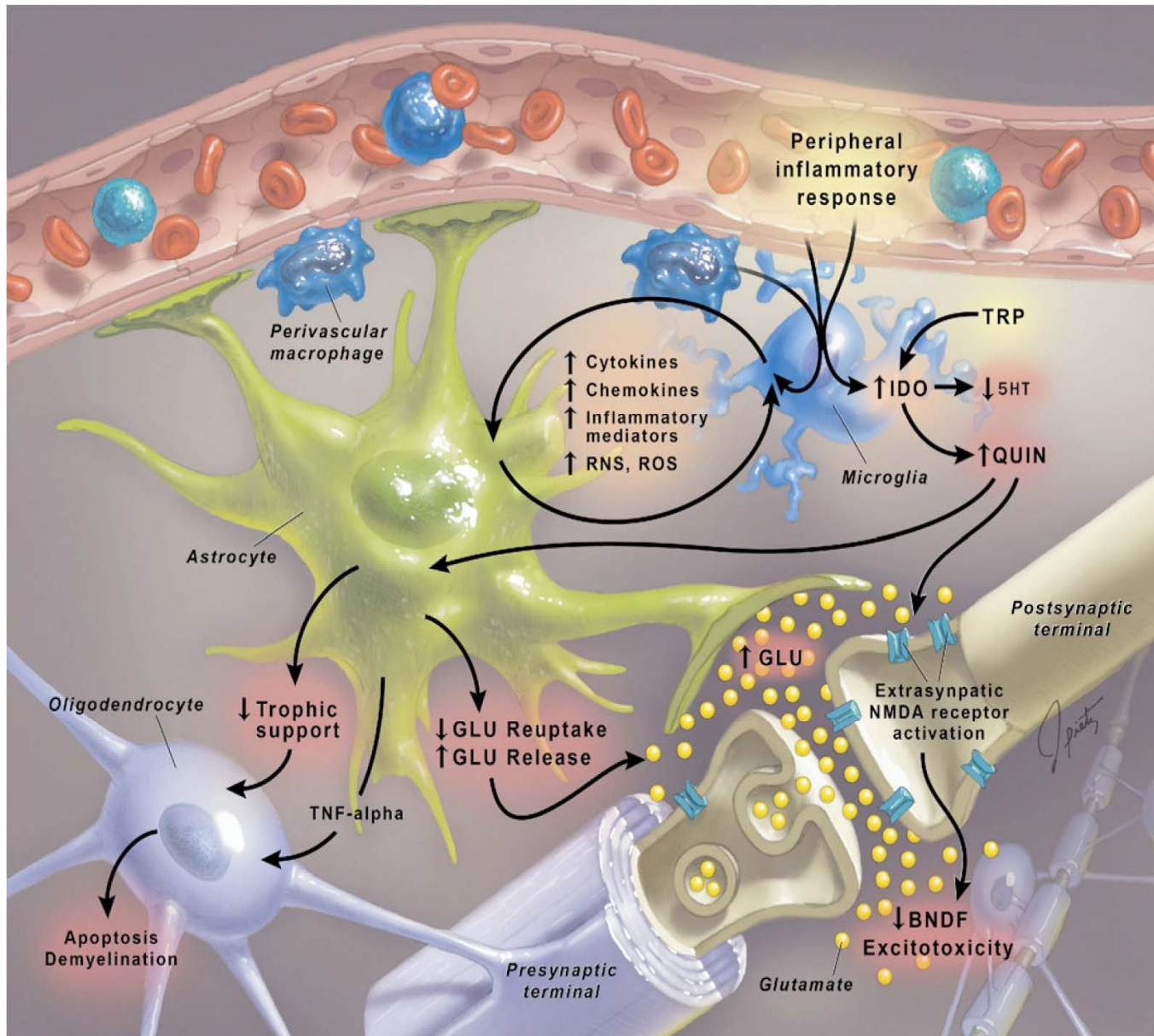
- A β is main component of SP in AD
- A β 42 is deposited early and A β 40 later in AD
- Diagnostically not useful, but maybe helpful for monitoring disease prediction and progression of AD and MCI?
- Sensitive measures in female and in MCI?

CNS Function, Inflammation and Immunity

Cognitive Dysfunctions
Neuropsychiatric Disorders,
i.e. Dementia (i.e., Mrazek, 2003)

Physiological Cytokine functions
Immune-modulator (Raison, 2006)
Neuromodulator (Schiepers, 2005)
Synaptic Plasticity
Learning and Memory (Stellwagen, 2006)







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Review

Evidence for a cytokine model of cognitive function

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Clinical Associations between Cytokines and Cognitive Performance

■ Cognitive Impairment / Dementia

- IL-1, IL-6 and TNF are associated with dementia in cross-section (i.e., Bruunsgaard, 1999; Holmes, 2003a)
- IL-6 (over 7 years; Weaver, 2002) and CRP (over 25 years, Schmidt, 2002) show prospective association with cognitive impairment and dementia
- Prospective Association between fibrinogen / IL-6 and cognitive decline over 4 years (Rafnsson et al., 2007)

■ Specific Neuropsychology in the Elderly: “*MEMO*” (Baune et al., 2008)

- IL-8 is associated with decreased memory, cognitive speed and motor function in the general elderly population
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Associations between Genes of Inflammation and Cognitive Decline

- **Dementia:** IL-1 α , IL-1 β , IL-6 Genes increase risk for AD (i.e., Licastro, 2003)
 - **Cognitive Development:** IL-6-572C allele (Harding, 2005) and IL-6KO mice are associated with impaired cognitive function (Braidia, 2004)
 - **Cytokine polymorphisms and Neuropsychology** in the general elderly population
 - IL-1 β ↓ (Memory), TNF ↑ (cognitive speed) (Baune et al, 2008)
 - IL-1 β ↓ (abstraction, attention) (Tsai, 2008)
 - **Specific Cytokine Genes** (i.e., TNF) are related to neurodegenerative and neuroprotective mechanisms relevant to cognitive performance
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Association between IL-8 cytokine and cognitive performance in an elderly general population—The MEMO-Study

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Association between genetic variants of IL-1 β , IL-6 and TNF- α cytokines and cognitive performance in the elderly general population of the MEMO-study

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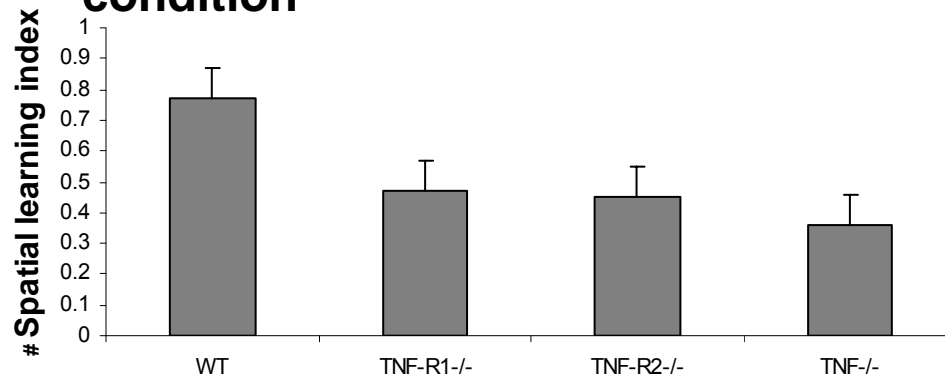
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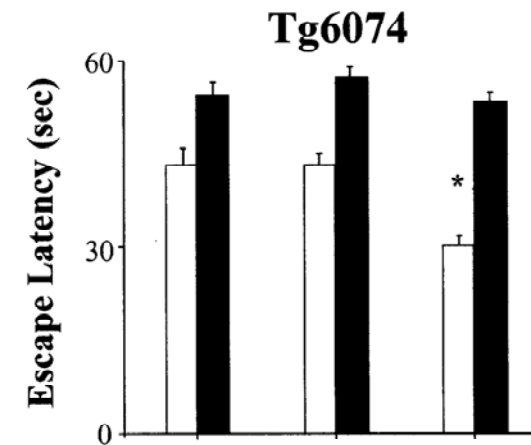
Physiological und Pathological Cognitive Function of TNF in mechanistic Studies

TNF: Immunological unstimulated condition



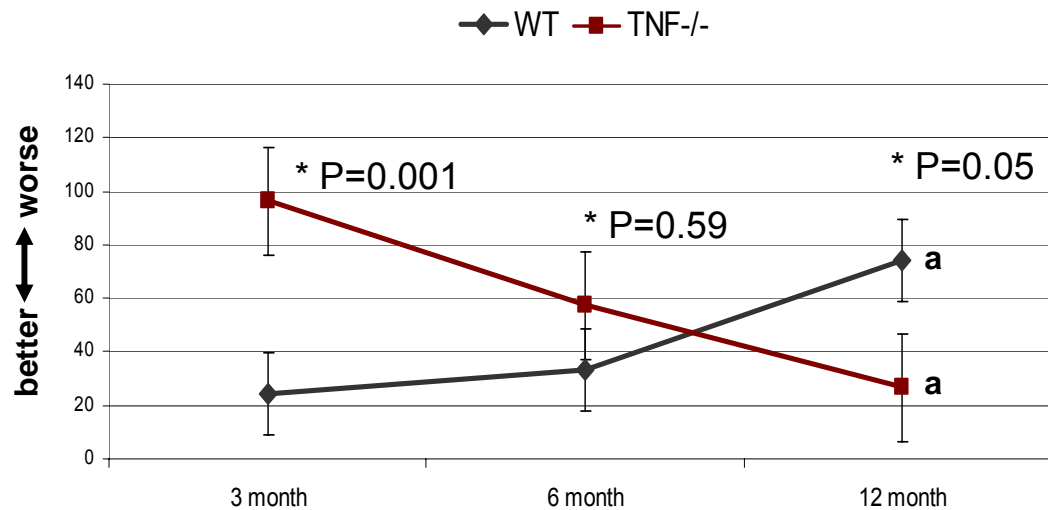
Baune et al., 2008 Mice strains on B.6 background

TNF over-expression



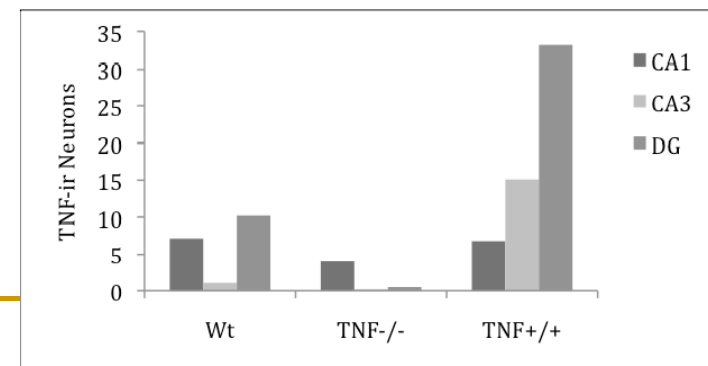
Fiore et al, 2000

TNF: Neurodevelopment and Aging



McAfoose...Baune et al., 2008

Hippocampus: TNF



Garner & Baune, in sub.



American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 147B:1056–1064 (2008)

Cognitive Dysfunction in Mice Deficient for TNF- and Its Receptors

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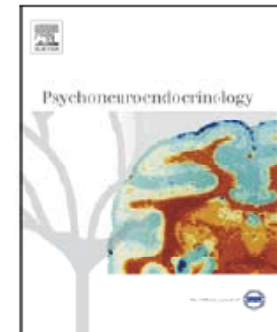


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SHORT COMMUNICATION

The effects of TNF deficiency on age-related cognitive performance

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PROOF

Plasma Proteins predict Alzheimer's disease

Table 1 Eighteen plasma signaling proteins that predict clinical Alzheimer's diagnosis

Predictors	<i>d</i> -score	<i>q</i> -value (%)
ANG-2	2.1	≤0.05
CCL5	-2.9	≤0.05
CCL7	-1.7	≤0.05
CCL15	-1.6	≤0.05
CCL18	1.9	3.1
CXCL8	1.7	3.1
EGF	-2.7	≤0.05
G-CSF	-1.9	≤0.05
GDNF	-1.8	≤0.05
ICAM-1	2.2	≤0.05
IGFBP-6	1.5	3.1
IL-1 α	-2.9	≤0.05
IL-3	-2.0	≤0.05
IL-11	2.1	≤0.05
M-CSF	-2.4	≤0.05
PDGF-BB	-3.4	≤0.05
TNF- α	-2.6	≤0.05
TRAIL-R4	1.8	3.1

In the training set, predictor discovery by PAM identified 18 predictors from the normalized array measurements of 120 signaling proteins. SAM was used to calculate *d*-scores indicating the relative positive (increased) and negative (decreased) changes in concentration of these proteins in plasma of subjects with Alzheimer's disease in comparison to NDC subjects. SAM calculates a minimal false discovery rate (*q*-value) for significance. ANG-2, angiopoietin-2. CCL, chemokine that contains a C-C motif; CXCL, chemokine that contains a C-X-C motif; G-CSF, granulocyte-colony stimulating factor; GDNF, glial-derived neurotrophic factor; ICAM-1, intercellular adhesion molecule-1; IGFBP-1, insulin-like growth factor-binding protein-6; IL, interleukin; PDGF-BB, platelet-derived growth factor BB; TRAIL-R4, TNF-related apoptosis-inducing ligand receptor-4.

Ray et al. (2007)

Summary and Outlook

- Inflammatory and immune markers are the most prominent proteins involved in cognitive decline and AD
- Peripheral markers reflect cognitive decline / functioning
- Cytokines play a role in AD pathogenesis via SP deposition and in very early stages of cognitive decline via direct / indirect effects on LTP, LDP, neurogenesis, neural plasticity
- Study of single inflammatory markers in isolation has limited validity

➔ **Multiple Marker Analyses are promising**
