Activation of the TWEAK/Fn14 Inflammatory Pathway in a Murine Model of Subarachnoid Hemorrhage

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EMORY NEUROSURGERY
“Early Brain Injury” after SAH

- Inflammation
- Cerebral Edema
- Cell Death
Inflammation after SAH

• Pro-inflammatory cytokines are found in the CSF after SAH

• There is a robust inflammatory response in animal models of SAH

• Inflammation may contribute to cerebral edema, cell death and vasospasm after SAH
Tumor Necrosis Factor-like Weak Inducer of Apoptosis (TWEAK)

- Member of the TNF superfamily
- Binds to the receptor fibroblast growth factor-inducible 14 (Fn14)
- Both TWEAK and Fn14 are expressed by perivascular astrocytes, endothelial cells and microglia
- TWEAK and Fn14 expression increase after injury
Inflammation via NF-κB pathway
Hypothesis

Inflammation via NF-κB pathway

Astrocyte

RBC

Neurovascular Unit

Inflammation via NF-κB pathway
Intra-luminal ICA Perforation Model

ECA

≈0.75 cm

ICA

CCA
After Transcardiac Perfusion

Sham-operated Control  Subarachnoid Hemorrhage
Tissue from ipsilateral parietal cortex was analyzed
Increased Fn14 Expression is Sustained 12-24 Hours after SAH

Fold Increase of Fn14 by Real-Time PCR

Western Blot / Protein Level

Fn14 mRNA Expression

control n=3  12 hr SAH n=3  24 hr SAH n=2

GAPDH
SAH Induces a NF-κB-mediated Inflammatory Reaction

- Monocyte chemorattractant protein-1 (MCP-1) is a proinflammatory chemokine
- MCP-1 and TNFα are NF-κB-mediated

Fold Increase of MCP-1 and TNFα mRNA Expression 6 Hours after SAH
Inhibition of TWEAK/Fn14 Reduces Inflammation after SAH

MCP-1 Induction 2 Hours after SAH

Intraventricular Injection of Evans Blue

mRNA Expression

SAH + n=4

SAH + Decoy n=4
Conclusions

- SAH causes a widespread TWEAK/Fn14-mediated inflammatory reaction in the brain

- Inhibition of TWEAK/Fn14 axis may have a therapeutic effect on early brain injury after SAH
Future Experiments

• Determine the source of TWEAK after SAH

• Inhibition of TWEAK/Fn14 with intravenous inhibitors

• Long-term outcomes with behavioral studies and cell death markers
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