SANDERS-BROWN CENTER ON AGING

UK UNIVERSITY OF KENTUCKY

From Concussion to Dementia: a Key Role for Dysregulated Brain Inflammation

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Learning Objectives

Upon completion of this educational activity, participants will be able to:

◆Describe the evidence that a prior head injury can increase Alzheimer's disease risk.

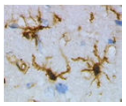
◆Discuss how abnormal brain inflammation is involved in neurologic impairment after traumatic brain injury.

◆Explain the importance of preventing and treating traumatic brain injury as a means to lower Alzheimer's disease risk.

Outline of Today's Presentation

- Overview of TBI as a risk factor for dementia

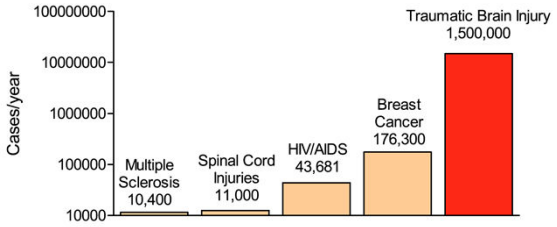
- TBI and dysregulated brain inflammation



- Targeting brain inflammation after TBI

TBI is the leading cause of death and disability in persons under 40 years of age

An increasing problem in the elderly due to falls; a major contributor to long-term neurologic impairments with associated medical costs and socio-economic burden. These alarming statistics are also anticipated to increase because of high incidence of head injuries sustained by military personnel, concussion-related sports injuries, and the increased incidence of falls due to aging of the global population.



TBI is a risk factor for AD

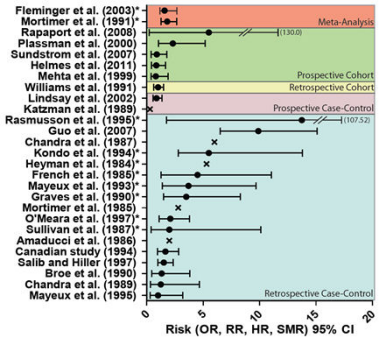


Figure 1. Risk between traumatic brain injury and Alzheimer's Disease with 95% CI, where available, from previous studies. Studies with crosses (X) did not provide 95% CIs. Studies marked with an asterisk (*) found a statistically significant association.

May et al., 2011, J Neurol Neurosci 2: 5-12

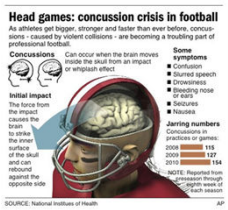
TBI is a risk factor for AD

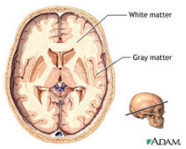
Table 1: Risk factors for Alzheimer disease

Factor	Risk (95% CI)
Systolic hypertension > 160 mm/Hg	RR: 1.5 (1.0-2.3)[4] OR: 2.3 (1.0-5.5)[5]
Serum cholesterol > 6.5 mmol/L	RR: 2.1 (1.0-4.4)[5] RR: 3.1 (1.2-8.5)[6]
Moderate wine consumption (250-500 mL/d) compared with more or less than this amount	RR: 0.53 (0.3-0.95)[7]
High level of physical activity* compared with little or no regular exercise	RR: 0.5 (0.28-0.90)[8] RR: 0.55 (0.34-0.88)[9] RR: 0.69 (0.5-0.96)[10]
Smoking, current	RR: 1.74 (1.21-2.50)[11] RR: 1.99 (1.33-2.98)[12]
Head injury, with loss of consciousness	
Moderate	HR: 2.32 (1.04-5.1)[13]
Severe	HR: 4.51(1.77-11.47)[13]
Education > 15 yr (v. < 12 yr)	RR: 0.48 (0.27-0.84)[14]
Statin drugs	RR: 0.82 (0.46-1.46)[15] HR: 1.19 (0.35-2.96)[16]
Nonsteroidal anti-inflammatory drugs	RR: 0.42 (0.26-0.66)[17] RR: 0.51 (0.37-0.70)[18]

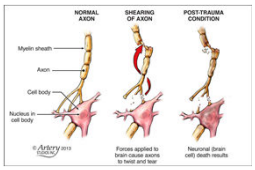
Patterson et al (2008) CMAJ 178: 548-556

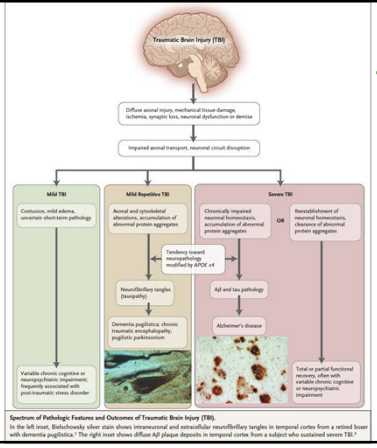
How might TBI increase the risk of AD?





- Brain tissue contains gray and white matter.
- Gray matter contains neuronal cell bodies & their supporting glia/capillaries. White matter contains bundles of myelinated axons.
- Gray and white matter are different densities, so movement of the brain causes shear forces at the gray-white matter interface.
- This can stretch, twist, or rupture axons.





Spectrum of Pathologic Features and Outcomes of Traumatic Brain Injury (TBI). In the left inset, Bielschowsky silver stain shows intraneuronal and extracellular neurofibrillary tangles in temporal cortex from a retired boxer with dementia pugilistica.[4] The right inset shows diffuse Aβ plaque deposits in temporal cortex from a subject who sustained severe TBI.[5]

Spectrum of pathological features and outcomes of TBI

Diffuse axonal injury leads to downstream pathologies.

AD-related pathologies such as NFT, APP and Aβ plaques.

Repetitive TBI can lead to Chronic Traumatic Encephalopathy (CTE).

NEJM 363:14 (2010)

CTE: A long term consequence of mild repetitive TBI

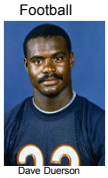
Clinical signs include memory impairment, emotional lability, aggression, speech and gait disturbances.

Gross pathology shows atrophy of the cerebrum, medial temporal lobe, thalamus, mammillary bodies and brainstem. Severe cases also have atrophy of the hippocampus, entorhinal cortex and amygdala.

Boxing

Mike Quarry

Football



Dave Duerson

Wrestling

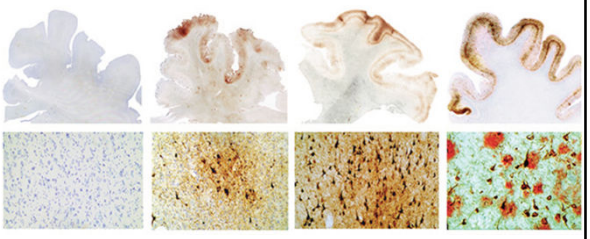
Chris Benoit

Hockey

Derek Boogaard

CTE neuropathology

CTE has some neuropathology features like AD, but is primarily a tauopathy, as only ~30% of subjects also have amyloid deposits at autopsy



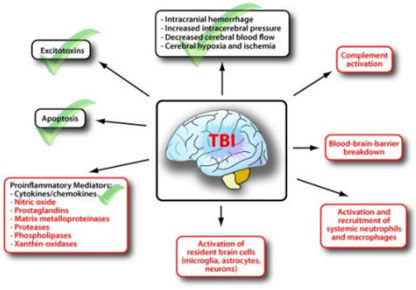
Normal | NFL player 1 | NFL player 2 | AD patient

Images from A. McKee, Boston Univ

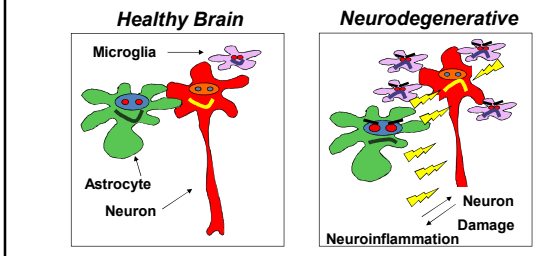
Neuropathology of CTE vs AD

CTE	AD
Primarily a tauopathy; only 30% of subjects also have amyloid deposits	Amyloid and tau deposits by definition
Patchy distribution in frontal and temporal cortices especially in sulcal depths	Begins in entorhinal cortex and spreads to limbic system and later to cortex
Tau accumulates in neurons, perivascular regions, and in astrocytes	Tau accumulations in neurons
Amyloid accumulations in gray and white matter	Amyloid accumulations in gray matter and cerebrovasculature
Tau and amyloid accumulation can be uncoupled	Amyloid precedes and is required for tau deposition
TDP-43 positive	TDP-43 negative

Another feature common to TBI, CTE, and AD: Dysregulated glial activation and neuroinflammation



The Janus Face of Glial Activation



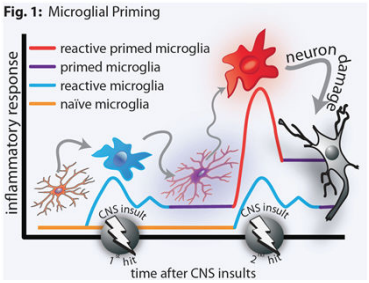
Glia respond to stimuli by undergoing activation ⇨ Normally beneficial

Chronic, unregulated glia activation ⇨ Detrimental neuroinflammation

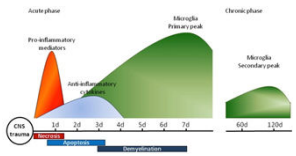
Dysregulated microglia: a mechanism for enhanced neuron damage after repetitive TBI?

Microglia priming: process by which a primary insult sensitizes the cell to exhibit exaggerated response to a subsequent stimulus.

Fig. 1: Microglial Priming



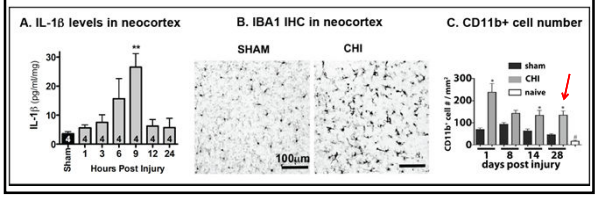
Dysregulated microglial activation and neuroinflammation in TBI



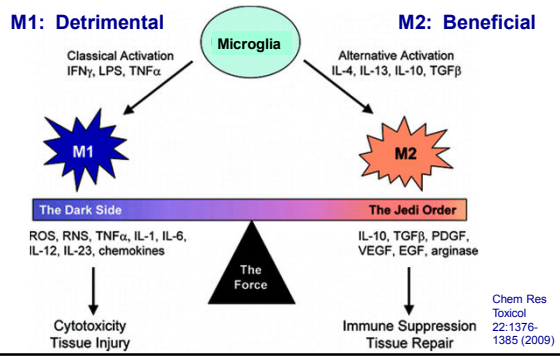
Human head injury induces a persistent microglial activation that lasts for months to years after injury

We also observe prolonged microglial activation in our mouse models of diffuse closed head injury

Midline CHI produces acute increases in IL-1β levels, morphological changes in microglia by IBA1 staining, and prolonged activation of microglia by CD11b labeling

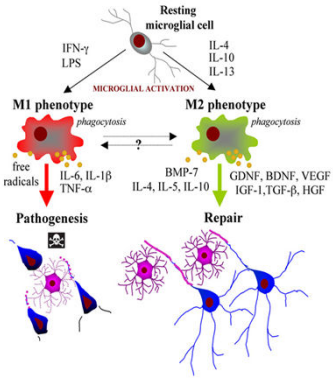


Brain inflammation is a balance between beneficial and detrimental responses



Chem Res Toxicol 22:1376-1385 (2009)

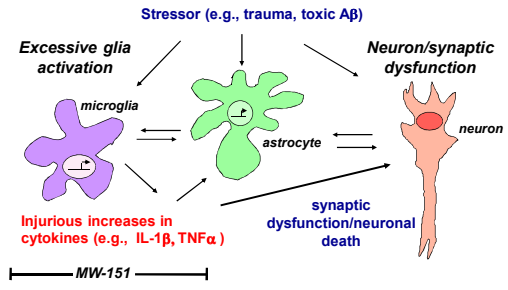
Microglia activation can be beneficial or detrimental



Frontiers in Biosci 16:2326 (2011)

Targeting the up-regulated cytokine – synaptic dysfunction cycle

Therapeutic Goal: attenuate pathology progression by appropriate dosing with intracellular signal transduction targeted small molecules

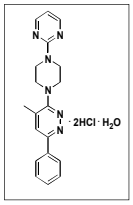


Example novel candidate with desired properties: MW-151

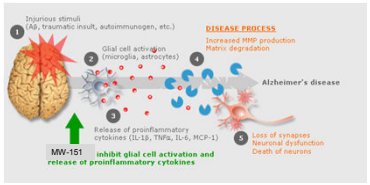
MW-151 compound has drug-like properties and is CNS-penetrant

Chico et al., 2009, Nature Rev Drug Discovery 8: 892; Hu et al., 2007, Bioorg Med Chem Lett 17: 414

MW-151

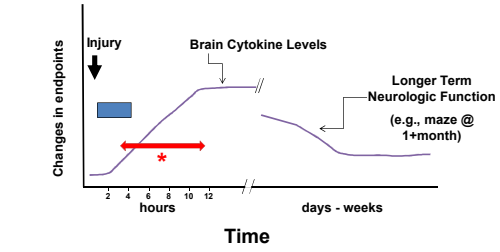


Mechanism of action: selective inhibition of injury-induced glial activation and proinflammatory cytokine overproduction



Targeting cytokine overproduction in closed head TBI mouse model screening

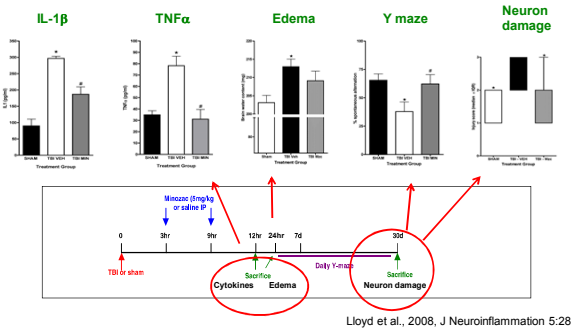
* ***Does post-injury compound treatment within delayed window yield modulation of the targeted process and desired neurologic outcomes?***



= time gap of injury-to-trauma center

Targeting brain inflammation post-injury is efficacious

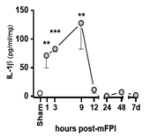
Reduces brain proinflammatory cytokine levels, brain edema, and downstream neurologic and behavioral impairments

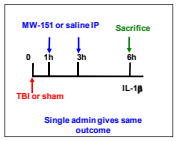


Lloyd et al., 2008, J Neuroinflammation 5:28

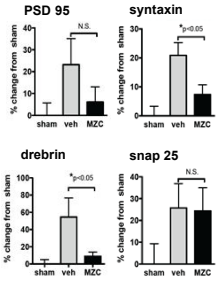
Post-injury treatment in a midline/central fluid percussion TBI model of diffuse axonal injury is also effective

Cytokine surge after TBI

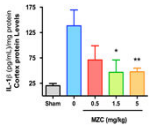




MW-151 prevents injury-induced synaptic changes



MW-151 suppresses injury-induced brain IL-1β levels



MW-151 is effective in animal models of other CNS disorders where proinflammatory cytokine increases contribute to pathophysiology

- **TBI models of closed-head, diffuse axonal injury:**
  Lloyd et al., 2008, J Neuroinflammation 5:28
  Bachstetter et al., 2013, unpublished
- **AD-relevant pathology models:**
  Hu et al., 2007, Bioorg Med Chem Lett 17:414
  Bachstetter et al., 2012, J Neurosci 32: 10201
- **EAE model:**
  Karpus et al., 2008, J Neuroimmunology 203:73
- **Seizure-induced neurologic sequelae:**
  Somera-Molina et al., 2007, Epilepsia 48:1785
- **Two-hit models:**
  Somera-Molina et al., 2009, Brain Res. 1282:162 (KA, KA)
  Chrzaszcz et al., 2010 J. Neurotrauma 27:1283 (TBI, ECS)

Summary and Conclusions

- **TBI is a major risk factor for development of dementia (AD and CTE).**
- **Dysregulated glial activation and brain inflammation may be one mechanism that contributes to neurologic/functional impairments after TBI.**
- **Targeting of selected activated glia functions (NOT pan-suppressors) is a viable drug discovery strategy with potential for disease modification.**

Acknowledgements

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alzheimer's association

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