PhD DEFENCE Thursday, March 1st, 2018
Student: Tom (Wai Hang) Cheng
Title: THE INTERACTION OF REPETITIVE MILD TRAUMATIC BRAIN INJURY, ALZHEIMER DISEASE AND AGEING
Time and location: 12:30pm PST; Room 200 of the Graduate Student Centre (6371 Crescent Road), UBC Vancouver Point Grey Campus
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ABSTRACT

Traumatic brain injury (TBI) is an important public health issue worldwide. It is strongly linked to neurodegenerative conditions such as Alzheimer's Disease (AD) and Chronic Traumatic Encephalopathy. Despite numerous promising pre-clinical studies, there is no effective clinical treatment for TBI, indicating inefficiency in translation of scientific research from bench to bedside.

This thesis thus attempts to address the issue through two approaches. Firstly, we reviewed the commonly-used pre-clinical TBI models, and found that many lack thorough biomechanical considerations. We thus developed a new mouse TBI model, Closed-Head Impact Model of Engineered Rotational Acceleration (CHIMERA). CHIMERA reproducibly induces clinically-relevant TBI, both in terms of biomechanics and neuropathology. CHIMERA mild TBI (mTBI) induces behavioural (e.g. neurological, motor, and cognitive), histological and biochemical changes (e.g. diffuse axonal injury, white matter microgliosis, and brain cytokine induction). We further demonstrated that CHIMERA mTBI outcomes are scalable by varying the mechanical inputs. These observations demonstrate that CHIMERA is a novel and valuable platform for TBI research.

Next, we induced CHIMERA mTBI in APP/PS1 mice, a transgenic model of AD amyloidosis, and characterised both acute and long-term consequences. Here we included two age groups of animals, as TBI occur in both the young and the old populations. In the acute phase, mTBI led to subtle and transient age-dependent changes in Aβ deposits. Age-at-injury and genotype showed complex interactions in determining microglial and cytokine outcomes, such that neuroinflammation was increased in old wildtype mice and young APP/PS1 mice. Age-at-injury also markedly affected neurofilament response, as neurofilament-positive axonal bulbs and plasma neurofilament-light levels were elevated in young mice, but not old mice, of both genotypes. In the chronic phase, mTBI led to prolonged white matter microgliosis and axonal injury up to 8-mo post-injury. MTBI also intensified long-term fear memory in APP/PS1 mice, reminiscent of post-traumatic stress disorder phenotypes.

In summary, we have developed a reproducible and clinically-relevant TBI model. We showed that genetic predisposition to AD and age-at-injury are both significant modifiers of acute and long-term mTBI outcomes. These findings may provide insights for future attempts in understanding the mechanistic pathways of TBI pathogenesis.