Final Report

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Date: 24 Oct 2017

Title of Project: Identifying biomarkers to predict Alzheimer's, dementia, and poor cognitive ageing.

Summary:
As the brain ages, it takes on a pro-inflammatory profile associated with priming of immune cells so that they become hyper-active. Aged individuals, even otherwise healthy ones, therefore respond to illness and infection with exaggerated immune responses that can be fatal. The brain's immune cells in ageing people are also more active under basal conditions, potentially resulting in excess pruning of neuronal synapses and even excess neuronal death. In this way, this neuroinflammatory ageing also contributes to cognitive decline.

Chronic central inflammation that commences earlier in life may trigger early neuroinflammatory ageing and contribute to impaired brain function, including impaired cognition, prior to old-age and may accelerate the onset of dementia. The chronic central inflammation associated with obesity is one such potential trigger.

Obesity is an inflammatory disease, with chronic low-grade central and systemic inflammation evident in humans and animal models. In our work, both three days and three weeks high fat diet in adult rats leads to increases in brain microglial activation. Obese humans similarly have brain gliosis. Remarkably, this obesity-associated neuroinflammation is highly similar to the profile seen in ageing rodent models and in humans.

Both obesity and ageing are associated with cognitive deficits, and brain inflammation may play a key role. In humans, the obese are more likely to have deficits in learning, memory and executive function than non-obese. In animal models, adult rats made overweight by neonatal overfeeding, and those fed a high fat diet, have very poor recall in tests of cognitive function. With respect to ageing, 9% of Australians over 65 and 30% over 85 have dementia. Another 10-20% at this latter age have mild cognitive impairment. Aged rats are also at risk of poorer cognitive function than their younger counterparts, showing ageing-related memory decline and being more susceptible to cognitive impairment by immune or other challenges. Such obesity- and age-associated cognitive deficits are improved with anti-inflammatories.

We, and others, have shown high fat diet can lead to brain inflammation with priming of the brain's immune cells to be more reactive to neuroimmune challenge. We therefore hypothesized that **obesity leads to brain inflammation that primes microglia to retain a pro-inflammatory or 'activated' state similar to that seen in the aged individual. We further hypothesized that these primed microglia would be hyper-active and would lead to brain cell remodeling to the detriment of cognitive function.**

Here we aimed to:

1) Determine if obesity leads to accelerated neuroinflammatory ageing in a rodent model and if this is linked to cognitive dysfunction.

2) Identify blood biomarkers in the rodent model that reflect degree of brain inflammation.

3) Establish if blood biomarkers of brain inflammation and cognitive dysfunction identified in the rat also predict degree of cognitive dysfunction and onset of dementia in ageing humans.

Our early results from this project suggest that:

Aim 1:

1) High fat diet alone, in young animals, does not influence microglial morphology and does not lead to cognitive deficits.
2) Ageing leads to a reduction in microglial complexity and increased microglial numbers consistent with microglial priming.
3) High fat diet in combination with ageing leads to cognitive decline.

We have also determined that high fat diet does not influence the appearance of amyloid beta plaques (indicative of Alzheimer's and cognitive decline) in the rat model. We see ageing and high fat diet-induced differences in the expression of microglial genes and genes related to inflammation (pro-inflammatory cytokines) and hypothesize functional changes in the microglia may contribute to ageing-related cognitive dysfunction in the presence of high fat diet.

Aim 2 and 3:

We have identified a specific biomarker, the protein for which is elevated with ageing in rat plasma and the gene expression for which is increased with ageing in rat hippocampus. This corresponds to hypo-methylation (indicative of reduced potential for transcription) in the rat hippocampus. Importantly, there is also hypo-methylation of the promotor region for this marker in human blood. We are still working to link these changes to cognitive performance in the human cohort.

Hypothesis vs Findings:

High fat diet can lead to increased microglial priming in the aged and this is associated with cognitive dysfunction, as we hypothesized. It is noteworthy that high fat diet does not lead to cognitive deficits in young animals. We have also identified at least one promising biomarker of cognitive decline in ageing.

Unanswered Questions:

- Are the effects of high fat diet on cognitive decline in ageing reversible upon return to a healthy diet?
- Are the effects of high fat diet in ageing on microglial morphology reflected in differences in function?
- What does our biomarker do in the context of diet and ageing, and can we suppress its expression to improve cognitive function?

What these research outcomes mean:
With an ageing and increasingly obese population, Australia is facing a significant increase in the proportion of its citizens suffering from cognitive dysfunction, including that associated with dementia and neurodegenerative disease. There is a clear need to discover the mechanisms behind how neuroinflammatory ageing contributes to cognitive impairment, and to develop the tools to prevent and treat it.

Our findings suggest that diet may play an important role in cognitive health when we age. For young individuals, unhealthy eating may not adversely affect memory, learning, or cognitive function. However, as we age, we may become very vulnerable to the adverse effects of a poor diet and suffer accelerated cognitive decline as a result.