Final Report

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Title of Project: Understanding how near infrared light protects against Parkinson's disease

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Summary:

While current therapies for Parkinson's disease (PD) can relieve some of the clinical signs and symptoms of disease, they do not prevent or even slow disease progression. Thus there is an urgent need for treatments that address disease progression; ideally treatments that are also safe, non-invasive, free from side-effects and simple to administer.

This project sought to understand how an emerging treatment option known as photobiomodulation (PBM) – the irradiation of tissue with low-energy red to infrared light – can protect against the brain against the damage associated with PD.

Our number of studies from our group using rodent models of PD have shown that PBM protects against damage to dopaminergic neural circuits in the brain and, as a result, prevents the movement impairment normally associated with the disease. This treatment has also proved effective in reducing damage to the central nervous system (CNS) in models of other diseases, including dementia, stroke and retinal degeneration.

At present, while the protective effects of PBM are well established, it is unclear exactly how this treatment works. Most previous work has assumed that PBM acts directly on the damaged tissue itself, inducing self-repair of damaged cells. However evidence from our research suggests that PBM is still effective at protecting the brain when targeted at peripheral tissues (e.g. a leg), suggesting that it stimulates some unidentified circulating protective 'factor(s)'.

Hypothesis vs Findings

The aims of this project were to confirm the neuroprotective effects of 'remote PBM' (i.e. light targeted at the body) relative to 'direct PBM' (i.e. light targeted at the head) and to gain insights into the mechanisms involved. One hypothesis leading into this work was the remote PBM triggers the proliferation of stem cells in the bone marrow,

specifically mesenchymal stem cells (MSCs), which could then be recruited to sites of injury to release growth factors that enhance the repair and survival of damaged nerve cells.

Modelling PD by injecting mice with a neurotoxin known as MPTP, we confirmed that remote PBM protected the brain against MPTP insult, and that the effectiveness of this protective treatment was comparable to that of direct PBM. Furthermore, we showed that *pre-conditioning* with remote PBM, where the treatment is only delivered in the days before the MPTP injections, also protects the brain from MPTP insult. Just one 90 second treatment per day for 10 days prevented any detectable damage to dopaminergic cell populations in the brain. Thus, the hypothesis that remote PBM can protect against brain damage in a model of PD was confirmed.

One hypothesis heading into the project was that the neuroprotective effect of remote PBM is mediated by bone marrow-derived MSCs. This proved difficult to assess in our mouse model, as there is considerable debate as to how to reliably identify MSCs from other bone marrow cells. Nonetheless, we developed a panel of 8 cell markers, for flow cytometry applications, that together appear to accurately identify mouse MSCs. Using this panel, we discovered that remote PBM produces a modest but significant increase in a sub-population of MSCs – while it appears that PBM can influence MSCs, more work is required to determine whether these cells are responsible for mediating the neuroprotective effects of PBM.

To gain an understanding of how PBM conditions brain tissue to be resilient against stressors, we performed an unbiased transcriptomic study to simultaneous assess all molecular systems in the brain. This revealed a range of molecular changes in pathways relating to control of transcription, stress responses and cell death. From this study we have identified a number of key molecules for follow-up validation by alternative approaches.

Unanswered Questions

While this project has provided a great amount of insight into the mechanisms by which PBM protects the brain, there are still many questions that remain to be answered, particularly with respect to remote PBM. For example, what specific peripheral tissues should be targeted for greatest efficacy? What should be the dose? Do the MSCs traffic to sites of damage within the brain? If so, how are they recruited, and how do they interact with damaged tissue?

Thanks to this generous gift from the Brain Foundation, we have been able to leverage the findings to obtain additional grant funding that will allow us to address a number of these questions. Various aspects of this work have been published in international journals and presented at scientific meetings, and form the basis of

several current research projects being undertaken by PhD and Honours students at the University of Sydney.

What these research outcomes mean

While these research outcomes are intriguing from a basic science perspective in terms of increasing our knowledge of the mechanisms underlying PBM-induced protection, their greatest promise lies in their clinical relevance. At presence, the use of PBM for the treatment of patients with PD or other brain diseases is limited by one major barrier – the lack of penetration of light energy across the thick human skull and superficial brain tissue. If we can build evidence that treating an easily-accessible peripheral tissue, such as a leg, is also effective in protecting the brain, then the problem of targeting light to deeply embedded sites in the brain becomes irrelevant. We will continue to vigorously pursue this line of research, as we strongly believe it has the potential to open novel therapeutic avenues for PD and other brain diseases that are currently lacking effective treatments.