Dissecting the balance of renewal and differentiation in human neural stem cells and their application to understanding neurological disorders

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Background

Neurodegenerative disorders and injuries causing brain damage including Alzheimer's disease and dementias often result in lifelong disabilities. Stem cells, with the ability to repair and replace damaged cells of the brain, including neural stem cells, may provide long-lasting therapeutic results. However, currently, we cannot produce suitable cells in sufficient quantities for the treatment of these disorders (i.e. dementia vs traumatic brain injury). By identifying and exploiting the factors influencing neural stem cells in normal and disease conditions, we can improve treatment strategies for the repair of neurodegeneration.

Brain damage and neurological disorders affect over 12% of Australians. Unfortunately, significant difficulties continue to limit the efficacy of stem cells in regenerative applications including in the treatment of the neurodegenerative disorders Alzheimer's Disease and dementias. To date, the isolation and characterisation of neural stem cells, along with poor survival, proliferation, integration and differentiation of the transplanted cells into the desired cell types, has so far resulted in little or no functional recovery. As such, the successful translation of stem cells to the treatment of these neurological disorders has tremendous socioeconomic importance and therapeutic potential.

The effective regeneration of brain tissue requires that the damaged cells be replenished as well as the integration of these cells with existing cells to form new functional neural networks. The isolation and expansion of human stem cells and limited neural lineage differentiation have provided the foundation for strategies in the treatment of neurodegenerative disorders. Potential models to overcome this include the multipotent mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs). Both of these cell types have a large capacity for self-renewal and differentiation into neural lineage cells i.e. we can isolate them in large numbers and expand them to provide cells of sufficient numbers to characterise for their suitability in therapeutic applications. In addition, these cells can contribute to the localised extracellular matrix and microenvironment that provides structural support and mediates numerous cellular functions. As such, these cells provide excellent models to derive large numbers of progeny as well as to examine lineage fate and the role of the microenvironment in mediating neurogenesis. More recently, our ability to examine and repair neurological damage has been augmented by the development of induced pluripotent stem cells (iPSCs) due to their immortilisation without compromise to their neural lineage (neurons vs astrocytes etc) potential. In particular, patient-derived iPSCs present the opportunity to overcome the current challenges associated with the use of stem cells in the repair of neurological disorders.

Hypothesis

Proteoglycans are crucial key regulators of the neural microenvironment and neural stem cell lineage commitment (differentiation). Using proteoglycans, we can identify and control the factors mediating human neural stem cell self-renewal and differentiation to produce lineage specific neural cells.

Aims

1. Confirm the importance of PGs to human neural stem cell (hNSC) regulation under basal and lineage-specific (neuronal, astrocyte and oligodendrocyte) culture conditions.
2. Targeting PGs to dissect the factors mediated by and interacting with PGs during neural lineage specific differentiation.
3. Develop lineage specific cultures for phenotypic analysis and functional characterisation.

Approaches

We will expand of iPSC-derived NPCs and patient-derived (Alzheimer's disease; AD) iPSCs and neural lineage differentiation of hMSCs, iPSC NPCs and AD iPSCs in neuronal and glial culture conditions, Cultures will be examined by cell culture, microscopy, immunocytochemistry and genetic sequencing approaches (transcriptome, RNASeq) to identify global and pathway specific markers to confirm the key role of PGs and their associated factors regulating the neural lineage profile of the cells. We will focus on PGs during lineage specific differentiation by altering their expression, cell and matrix interactions to improve differentiation efficiency. This will include targeting PGs in 2D and 3D cultures, to improve their lineage specificity.

References

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