Development of 3D human neural stem cell models for precision medical interventions in the treatment of brain injury and neurodegenerative disorders including AD and dementias.

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Background

As the second leading cause of death in Australia, the most prevalent form of dementia, Alzheimer's disease (AD), affects over 55 million people worldwide – a figure projected to rise sharply in the coming decades. Despite significant effort, successful treatments remain elusive. This is because current diagnostics fail to detect AD in its prolonged preclinical stages, when interventions are most effective. Therefore, there is an urgent need for accurate models to identify novel biomarkers to assess AD risk, identify and screen new drug targets and facilitate innovative treatments.

Our current understanding of AD is characterised by limited genetic risk genes. Biologically, dysregulated amyloid precursor protein (APP) processing, leads to the formation of amyloid beta (Aβ) plaques and hyperphosphorylated Tau protein tangles (Tau), resulting in neuronal atrophy. While Aβ and Tau pathologies are well-characterised in symptomatic stages, accumulating evidence suggests that disruptions in neurogenesis and dysfunctional glia may precede their onset, representing overlooked but potentially critical pathogenic drivers.

Heparan sulfate proteoglycans (HSPGs), key participants of the neural microenvironment, regulate neurogenesis via modulating growth factor signalling and neural stem cell (NSC) fate decisions, and also contribute to Aβ dysfunction. In this project we will leverage accepted and emerging genetic signatures in conjunction with our biologically relevant three-dimensional (3D) *in vitro* AD and stem cell culture models to explore neurogenesis, glial-neuronal interactions and its molecular dysregulation in AD.

Human stem cells offer a powerful platform to investigate the mechanisms mediating human neurogenesis, AD and neurodegeneration including multipotent mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs). These cells 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. 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

We hypothesise that in combination with genotype, epigenetic regulation of HSPG matrix proteins governs neural lineage fate and glial activation, and that dysregulation of this network contributes to the emergence of reactive astrocytes and susceptibility to AD. Biologically relevant 3D models allow us to interpret these interactions at the earliest stages of disease and provide a screening model for new and novel interventions.

Aims

Aim 1: To develop 3D hydrogel-based human neural models incorporating AD disease relevant genotypic differences.
Aim 2: Define the temporal dynamics and functional roles of DNA methylation during lineage specification and reactive gliosis.
Aim 3: Identify upstream regulatory networks controlling HSPG expression using integrated multiomic approach.
Aim 4: Evaluate small molecule modulators of astrocyte reactivity and validate HSPG biomarkers for translational relevance.

Approach

We propose a new approach to AD risk assessment that integrates genetic, epigenetic and cellular phenotypes to better reflect the multifactorial nature of disease susceptibility. Current models that rely solely on genetic risk and pathological factors fail to capture the dynamic influences of the ECM and cellular pathogenesis prior to the appearance of clinical symptoms. Our proposed framework addresses this gap by incorporating DNA methylation as a responsive biomarker of AD risk, with data from our 2D models demonstrating how distinct risk profiles differentially impact neural cell types and cell-cell and cell-matrix interactions.

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