Modelling the microenvironment of Parkinson's disease for drug-screening and regenerative purposes

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Abstract:
Parkinson disease (PD) is the second most common neurodegenerative disorder, linked to movement deficits due to intracellular deposition of alpha-synuclein (aS) in dopaminergic neurons of the basal ganglia and substantia nigra. PD is characterized by alterations in different types of brain cells, as well as in their extracellular matrix (ECM), e.g. expression of collagen, glycans (e.g., hyaluronan, HA)[1] and proteoglycans (e.g., chondroitin sulphate, CS).[2] In order to mimic this degenerative microenvironment, we are developing (glyco)peptide amphiphiles that spontaneously form supramolecular nanofibers, and gel under physiological conditions, copycatting the bioactivity of the main components of the brain ECM. We synthesised Fmoc-FF-glucosamine-6-sufate (GlcN6S) that spontaneous self-assemble into nanofibers (and mimic CS) and gel under the physiological environment. We loaded these hydrogels with neuronal cells, and we show that they can maintain astrocytes and microglia cultures, however, they are not able to maintain cultures of neurons. We are combining Fmoc-FF-GlcN6S with HA and their mimics, e.g., Fmoc-FF-glucosamine (GlcN), to better copycat of the brain/PD microenvironment. In parallel, we are increasing the complexity of the whole system by integrating a blood-brain barrier (BBB) model (TEER values up to 120 $\Omega.cm^2$) generated by the combination of endothelial cells, astrocytes and pericytes. Moreover, we are also developing brain organoids consisting of neurons and astrocytes that, through the addition of pre-formed aS fibrils, mimic the most relevant PD hallmark, i.e. intracellular deposits of aS. The loading of these organoids in the ECM-mimicking hydrogels is ongoing to generate a more complete PD microenvironment. Overall, our results indicate that it is possible to formulate a PD in vitro model that can be used for drug-screening applications as well as to devise strategies that can lead to the regeneration of the regions of the brain affected by PD.

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