In vitro modeling of dysfunctional glial cells in neurodegenerative diseases using human pluripotent stem cells

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Most neurodegenerative diseases are characterized by a complex and mostly still unresolved pathology. This fact, together with the lack of reliable models, have precluded the development of effective therapies counteracting the disease progression. In the past few years, several studies have evidenced that lack of proper functionality of glial cells (astrocytes, microglia and oligodendrocytes) has a key role in the pathology of several neurodegenerative conditions including Alzheimer´s disease, amyotrophic lateral sclerosis and multiple sclerosis among others.

However, this glial dysfunction is poorly modelled by available animal models, and we hypothesize that patient-derived cells can serve as a better platform where to study this glial dysfunction. In this sense, human pluripotent stem cells (hPSCs) has revolutionized the field allowing the generation of disease-relevant neural cell types that can be used for disease modelling, drug screening and, possibly, cell transplantation purposes.

In the case of the generation of oligodendrocytes (OLs) from hPSCs, we have developed a fast and robust protocol to generate surface antigen O4-positive ($O4^+$) and myelin basic protein-positive OLs from hPSCs in only 22 days, including from patients with multiple sclerosis or amyotrophic lateral sclerosis. The generated cells resemble primary human OLs at the transcriptome level and can myelinate neurons *in vivo*. Using *in vitro* OL-neuron co-cultures, effective myelination of neurons can also be demonstrated. This platform is being translated as well to the generation of the other glial cell types, allowing the derivation of patient-specific glial cells where to model disease-specific dysfunction.

This methodology can be used for elucidating pathogenic pathways associated with neurodegeneration and to identify therapeutic targets susceptible of drug modulation, contributing to the development of novel and effective drugs for these devastating disorders.

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