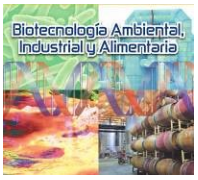
Poster



Preclinical evaluation of the safety and potency of neural stem cells from the germinal zone (Gz-NSC) for the treatment of intraventricular hemorrhage (IVH) consequences

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ABSTRACT

Motivation: Intraventricular hemorrhage (IVH) is a common cause of morbidity and mortality in premature infants with no available treatment. After IVH, there is a rupture of the germinal zone into the ventricles that entail the loss of neural stem cells (Gz-NSC). These Gz-NSC can be retrieved from the cerebrospinal fluid (CSF) of IVH patients, obtained after the therapeutic neuroendoscopic lavage performed in these patients to decrease intracranial pressure and that is usually discarded. We have found that Gz-NSC have the potential to differentiate into neuroblasts, oligodendrocyte precursors and few astrocytes when grafted into human brain organoids from iPSCs and mouse brains (1,2). We are evaluating the safety and efficacy profile of CSF-derived Gz-NSC in order to develop a cell therapy for IVH patients.

Methods: To examine the differentiation potency of Gz-NSC, we used immunofluorescence assays, fluorescence microspy techniques and computer analysis (ImageJ) to expand previous data, increase sample size, and quantify cell differentiation of grafted Gz-NSC cells in mouse brains and human brain organoids derived from iPSCs.

To study the safety profile, flow cytometry assays were carried on to analyze Gz-NSC cell proliferation (Ki67) and immunogenicity (CD80,CD86,CD40, major histocompatibility complex class II (MHC-II)).

Results: Based on the immunofluorescence assays, we have found less cells expressing doublecortin, an immature neural protein, and more cells expressing parvalbumin, an interneuron marker, in human brain organoids compared to animal models, suggesting that host can influence cell fate.

On the other hand, in order to study the immunogenicity of the Gz-NSC (safety profile), we have analyzed the expression of MHC-II and co-stimulatory molecules (CD80, CD86, CD40) in Gz-NSC before and after in vitro differentiation. Flow cytometry assays revealed Gz-NSC do not express co-stimulatory molecules and express different levels of MHC-II that are reduced when differentiated in vitro, which decreases the probability of an immune response in a future Gz-NSC based cell therapy

Conclusions: Taking into account that Gz-NSC have the potency to differentiate to a wide range of cerebral cell linages in both, human organoids and animal models, and are weakly immunogenic, an autologous Gz-NSC cell therapy could be a promising opportunity for IVH patients to overcome some of the neurocognitive problems associated to their condition.

REFERENCES

Fernandez-Muñoz, B.; Garcia-Delgado, A.B.; Arribas-Arribas, B.; Sanchez-Pernaute, R. Human neural stem cells for cell-based medicinal products. Cells 2021, 10, 2377*Brain Res. Mol. Brain Res.*, **110**(Suppl. 1), 76–84.

García-Delgado AB, Campos-Cuerva R, Rosell-Valle C, Martin-López M, Casado C, Ferrari D, et al. Brain Organoids to Evaluate Cellular Therapies. Animals. 2022;12(22):1–13