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Multiple sclerosis (MS) is an autoimmune disorder, unlike the two previous illnesses, in which T and B immune system cells induce widespread demyelination of the central nervous system, reduce the number of oligodendrocyte cells and degenerate neuronal axons. This is initiated when immune system cells recognise the myelin sheath as foreign causing them to secrete antibodies and pro-inflammatory cytokines in response.

In certain circumstances, CD4+ T cells also enter the internal nervous network which stimulates additional structural inflammation (encephalomyelitis), identified by the scarring of white matter and inflammation of the spinal cord. MS and experimental encephalomyelitis, the equivalent experimental model, are both classified as neurodegenerative disorders whereby inflammation within the brain and spinal cord closely correlates with axonal demyelination. Considering their likeness, I propose that experimental encephalomyelitis could act as a potential alternative to MS when examining the pre-clinical efficacy of stem cell-based therapies which aim to alleviate axonal degeneration. This conception was explored further in one study in which adipose-derived mesenchymal stem cells were manipulated to perform autologous cell transplantation into rodents afflicted with encephalomyelitis. This particular lineage was selected due to the stem cells' propensity to form late-stage heterodimer bonds with Integrin beta-1, enabling the transplanted cells to remain in the encephalomyelitis-affected regions of nervous system. From another perspective, one could theorize that this heterodimer bond would prevent further autoimmune response by blocking VLA-4 antigens on T cells which allow autoreactive lymphocytes to enter the brain. Following the culture of the adipose stem cells in '

Dulbecco’s modified Eagle’ formula, transfection with a plasmid encoding for fluorescent luciferase and secondary culture in HB-EGF, they were injected into model rats. The ‘ Eagle’ formula was specifically adopted to enhance the multilineage plasticity of the mesenchymal stem cells in order for them to suit two main functions; one role which results in the modulation of autoreactive MOG-T lymphocytes, and another role which manipulates the stem cells to secrete fibroblast growth factor and ciliary neurotrophic factor.

However, I argue that the most important stage of culture was the secondary step in which the stem cells were immersed in heparin-binding EGF growth factor. This stage played a salient role in converting non-adherent stem cells into a neurotrophic phenotype, ensuring that the correct neural growth factors were secreted post-transplant. Approximately two weeks after the transplantation, immunohistochemical analysis confirmed that spinal cord inflammation significantly decreased, accompanied by a lower rate of demyelination in comparison with the control group of mice (see Fig. 8, F and G). I believe that this is direct result of how the stem cells continued to secrete ciliary neurotrophic factor five weeks after the initial transplant which would have accelerated the activation rate of oligodendroglial progenitors. After observing the post-mortem tissue of the rodents, I think that the effect of this was resounding as axonal density in the spinal cord almost returned to similar levels before the onset of encephalomyelitis in the mice. In criticism of this therapy, the in-vivo secretion of proinflammatory cytokines within the rodents did not significantly change over the trial.

This raises a degree of uncertainty as to how the inflammation of the spinal cord reduced by such a large extent. Interestingly, further investigation revealed that the T-cells actually enhanced their production of Interleukin-4, 5 and 10 after stem cell integration. These strains of Interleukin are closely correlated with ‘ Th2’ T cell activity which indicates that the stem cells supported the anti-inflammatory T lymphocyte humoral response. Considering this, I believe that the adipose stem cells not only decreased the number of autoreactive MOG-specific T-cells but favoured the inflammatory-inhibitory Th2 cells. Acknowledging that MOG T cells induce manifestations of optic nerve and spinal cord lesions, one could argue that this therapy would suit both short-term neuroinflammation and long-term spinal cord repair. In summary, I think that these data sets are exemplar studies of how adipose-derived mesenchymal stem cells can conduct a bimodal function; through stimulating internal neurogenesis and suppressing autoimmune response via Th2 proliferation. Furthermore, the adipose stem cells proved particularly efficient at migrating through the blood-brain barrier and into the spinal cord, indicating that this therapy is transplant-suitable for neuroinflammatory disease. While this study illustrates how adipose stem cells can suppress lymphocyte activity, I believe that the main challenge of stem cell therapy for MS lies in initiating remyelination.

Initiating remyelination was explored in another study in which iPs cell derived-oligodendrocytes proved partially able to restore axonal myelination within hypo-myelinated mice subjects. While this achieves what Constantin G. et al. were unable to, in my opinion their 120-day stem cell culture protocol is not practically viable. This issue of culture longevity led another

group of researchers to continue with this line of research, aiming to reproduce the results of the previous inquiry but by using a faster and more efficient cell maturation protocol.

To achieve this, Douvaras P. et al. adopted the previous mechanism of oligodendrocyte maturation but notably decreased the time required for culture to 75 days, whilst boasting up to a 70% success rate. In order to examine how effective the progenitor cells were at stimulating remyelination, one must examine how their forebrains changed over the therapy. In fact, to accurately replicate the structural environment of an MS patient each of the rodents carried the shi/shi mutation resulting in severe myelin deficiency. By the end of week 12, 34. 4% of the stem cells had migrated to and remained within the corpus callosum, and approximately double this amount by week 16. I think that these readings are very encouraging as I can infer that the stem cell derived-progenitors largely remained within the inflamed area rather than migrating elsewhere within the brain.

Perhaps more importantly, the iPs-cell derived progenitors did not induce tumorigenesis by week 16, while 31% ± 3% of the axons within the corpus callosum had gained myelin sheath. One could hypothesize that this would resultantly offer symptomatic relief for MS patients, spanning from ocular regeneration to reduced paraparesis. In summary, I believe that these iPS-cell derived progenitors proved very capable of inducing progenitor differentiation in vivo, and at establishing dense myelin around neurons within the affected forebrain regions. While this proof-of-principle study

illustrates how myelinogenic oligodendrocytes can advance MS patient-specific stem cell therapies, I argue that the advanced stem cell differentiation protocol is the most significant development made over the course of these studies.