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Anti-inflammatory action of erythropoietin releasing neural precursors transplanted in a murine model of Parkinson's Disease

Parkinson's Disease (PD) is a common neurodegenerative disorder whose treatment is only symptomatic, as it does not block progressive degeneration of dopaminergic neurons in the Substantia Nigra. To overcome this, cell therapies have long been considered a feasible regenerative approach. Erythropoietin-releasing Neural Precursors (Er-NPCs) are SVZ-derived neural progenitors with neuronal differentiation capability. Here, we aimed to investigate the therapeutic effect of Er-NPCs transplantation in an *in vivo* model of PD focusing on functional recovery mediated by their anti-inflammatory effects.

Dopaminergic degeneration in C57BL/6 mice was obtained through the administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine following our already validated protocol. $1x10^5$ cells were infused in the mouse's left striatum following stereotaxic coordinates. Functional recovery was assessed by means of behavioral tests (horizontal and vertical grid tests) for a month. Animals were perfused 24h and 2 weeks after transplantation for immunohistochemistry studies and RNA expression analysis.

Our results show that animals grafted with Er-NPCs achieved remarkable functional recovery three days after transplantation. With immunofluorescence staining we observed that >70% of transplanted Er-NPCs were vital. A rapid anti-inflammatory effect was evident 24h post-transplant with the decrease of pro-inflammatory cytokines (e.g. IL1beta). This was maintained for the two weeks' observational period. At the same time, we observed a M1 to M2 macrophage switch. Co-injection of Er-NPCs with anti-EPO antibody neutralizes the anti-inflammatory effect, strongly indicating that this is mediated by Er-NPCs derived EPO.

In conclusion, this study confirms the therapeutic potential of Er-NPCs and suggests that these cells can counteract the neuroinflammatory processes typical of neurodegenerative disorders.