Host Responses to Human Neural Cell Therapy in Spinal Cord Injury

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ABSTRACT

Spinal cord injury (SCI) is a devastating condition without a cure. The SCI process comprises an initially mechanical trauma and a secondary cascade of events including a robust inflammatory and immune response. Experimental neural cell therapy in animal models have presented a series of beneficial effects such as neuroprotection, cell replacement, remyelination and axon regeneration. However, it is still to a large degree unclear how the host immune and nervous system respond to and interact with human donor neural stem/progenitor cells (NPCs). Therefore, features of human NPCs and their effects on potential host responder cells such as lymphocytes, microglia and spinal cord neural cells were studied in vitro and in vivo.

Features of two relevant types of donor human NPCs: human embryonic stem cell-derived NPCs (hESC-NPCs) and human fetal spinal cord-derived NPCs (hfNPCs), cultured under equivalent conditions were evaluated. hESC-NPCs and hfNPCs presented relatively similar expression patterns of human leukocyte antigen, co-stimulatory and adhesion molecules and were mostly not affected by two inflammatory cytokines of interest in SCI. Unstimulated hfNPCs secreted more transforming growth factor-β (TGF-β) but similar level of interleukin (IL)-10 compared to hESC-NPCs. In contrast to hfNPCs, hESC-NPCs showed increased release of TGF-β and IL-10 under in vitro conditions mimicking inflammation. Both human NPCS reduced an alloreaction between non-compatible allogeneic peripheral blood mononuclear cells (PBMCs) and up-regulated CD4⁺CD25⁺forkhead box P3” T cells, identified as induced regulatory T cells. However, hESC-NPCS but not hfNPCS dose-dependently triggered allogeneic PBMC proliferation, which may be at least partly due to TGF-β signaling. To conclude, differences in immunocompetence and interaction with allogeneic PBMCs were observed between hESC-NPCs and hfNPCs. These differences may be crucial for the host response in neural cell therapy.

To study the interaction between human NPCs and allogeneic microglia, an in vitro co-culture model was employed. The presence of microglia enhanced the survival and proliferation of hfNPCs, but hindered their differentiation. In the presence of hfNPCs, the survival, proliferation and phagocytosis of human microglia was increased. The expression of the neuroimmunoregulatory protein CD200 on hfNPCs, and the CD200 receptor on microglia, were enhanced in co-cultures, accompanied by increased secretion of TGF-β, indicating an anti-inflammatory feature of the co-cultures. To conclude, in this model of the naïve encounter of human donor NPCs with host microglial cells, the interplay between human NPCs and allogeneic microglia significantly affected their respective proliferation and phenotype. The neural cell and microglial interaction presented features that may benefit host neuroprotection and repair.

To further study host responses in neural cell therapy, hfNPCs were xenotransplanted to rats with severe or moderate SCI with or without immunosuppression. hfNPCs, expanded in vitro for 5 passages (NPC-P5) and grafted acutely to severe SCI rats, were completely rejected. In acute transplantation of NPC-P0 and delayed transplantation of NPC-P5 to rats with moderate SCI, a complete rejection occurred in 40 and 33%, respectively. Locomotor function was not significantly different between groups, indicating that neither transplantation nor rejection altered functional outcome during the 6-week long study. Host microglial activation at the SCI epicenter was reduced in hfNPC transplantation groups compared to lesion alone in both a xenogenic and allotransplantation model. In conclusion, human neural transplantation may result in a host rejection but still reduce the microglial response at the SCI epicenter.

Finally, the injured spinal cord response to human NPCs was evaluated in two different rat SCI models and a human allograft in vitro model. Spinal cord-derived hfNPCs (SC-NPCs) transplanted subacutely after contusion injury improved host locomotor function. In a compression SCI model, acutely or subacutely grafted SC-NPCs, but not chronically transplanted SC-NPCs or subacutely grafted forebrain-derived hfNPCs, enhanced functional recovery. Four months after transplantation, the number of surviving host spinal cord neurons was highest in acutely and subacutely transplanted groups, accompanied by the best hindlimb function. This suggests that transplanted SC-NPCs improve functional recovery by a neuroprotective effect. In addition, grafted SC-NPCs reduced the percentage of injury-induced apoptotic cells in a human organotypic spinal cord culture system.

In summary, human NPCs exert immunomodulatory and neuroprotective effects in SCI models. The human NPC origin, the host injury severity and the time point of neural cell therapy in SCI may affect the host--donor interaction and host response. With increased knowledge and awareness of these factors, human neural cell therapies for SCI can be improved to achieve higher therapeutic efficacy.

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