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SPINAL CORD

Making new connections

> human NSCs grafted into cervical SCI in rhesus monkeys extend axons into the host spinal cord

Grafting neural stem cells (NSCs) to sites of spinal cord injury (SCI) in rodents results in the formation of new neuronal relays across lesions, but whether this technique translates to humans is unclear. Rosenzweig et al. now show that human NSCs grafted into cervical SCI in rhesus monkeys extend axons into the host spinal cord and form synaptic connections with host circuits.

In this study, nine adult male monkeys received right-sided C7 hemisection lesions into which, 2 weeks later, 20 million human multipotent NSCs expressing GFP were grafted. Monkeys were euthanized between 2 and 9 months later and the spinal cord sectioned for analysis. Grafts did not survive, or failed to fill the lesion, in the first four monkeys assessed, leading the authors to optimize their rodent-centred grafting method for monkeys. Grafts survived and filled the lesions in the next five monkeys, 2–9 months after grafting, and the authors assessed their effect on the spinal cord.

Cells in the graft expressed markers of neuronal cells (~57% of cells), astrocytes (~26% of cells) and oligodendrocytes (~17% of cells). Furthermore, up to 150,000 axons derived from the graft were present 2 mm caudal to the lesion and a similar number emerged rostrally from the graft. Axons extended up to 50 mm from the graft, travelling primarily through white matter tracts. Although axons were immature and unmyelinated, they formed excitatory synapses with host neurons in the spinal cord caudal to the lesion.

Having shown that human NSC grafts can extend axons at the SCI, the authors determined if host axons extended into the human grafts; both of these events are necessary to re-establish a neuronal relay across the primate SCI. Indeed, grafts contained axons expressing a marker that was not expressed by graft-derived axons. Further experiments revealed that serotonergic axons and corticospinal axons penetrated the grafts; corticospinal axons, which are important for voluntary movement in humans, penetrated the graft by up to 500 µm.

As neural circuitry for hand control is located below the lesion imposed on monkeys (note that axons extending from the graft reached this location), the authors had assessed monkeys to see if grafts improved their motor function. All nine monkeys showed a partial spontaneous improvement in hand control in the 4–8 week period following lesions. However, only the five monkeys with a surviving graft saw additional improvement 10 weeks after lesion; for example, object manipulation scores for four out of five of these monkeys recovered to >25% and all five monkeys showed an improved performance over those with unsuccessful grafts in an overall measure of motor function.

The fact that human NSC grafts re-establish a neuronal relay across spinal cord injury in monkeys, coupled with the observations that tumours were not detected in subjects, graft cells did not migrate from the lesion and grafts could be visualized in vivo by magnetic resonance imaging, support the idea that NSC graft therapy has the potential to treat SCI in humans.

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ORIGINAL ARTICLE Rosenzweig, E. S. et al. Restorative effects of human neural stem cell grafts on the primate spinal cord. *Nat. Med.* https://doi.org/10.1038/nm.4502 (2018)