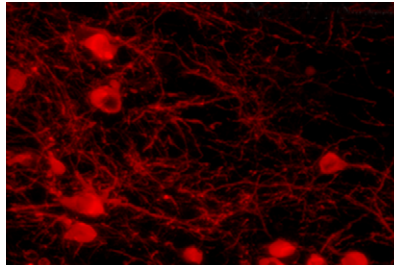


Transplantation of embryonic stem cells in Parkinson's disease

Researchers at Harvard Medical School (Boston, MA, USA) have shown that when low doses of embryonic stem cells are transplanted into the rat striatum, some of these cells develop into fully-differentiated dopaminergic neurons. Although this research is still in its preliminary stages, it could have significant implications for the treatment of Parkinson's disease.

Lars Björklund and colleagues injected a small number of embryonic stem cells (1000–2000) into the right striatum of 25 rats with Parkinson-like symptoms experimentally induced by intracerebral injections of the neurotoxin 6-hydroxydopamine. Several weeks later, five of the rats had developed teratoma-like tumours and six showed no graft survival. But 14 (56%) of the animals had graft-derived, functionally-integrated, dopaminergic neurons in their striatum. Furthermore, motor function gradually recovered in these animals to a significant degree in the 9 weeks following transplantation (*Proc Natl Acad Sci USA* 2002; **99**: 2344–49).

“Previous work in our lab has shown significant numbers of dopamine neurons from grafted embryonic stem cells, but due to the



Fully differentiated dopaminergic neurons?

Courtesy of Lars Björklund

high number of embryonic stem cells grafted, they also had numerous other types of cells”, says Björklund. “In our latest study, we were able to get rid of such unwanted cells [by using a lower dose of embryonic stem cells], which allowed the dopamine cells to functionally integrate and extend axons in the target area.”

While the experiment by Björklund's team showed that embryonic stem cells can develop into functional dopaminergic neurons in

the brain, the results are far from perfect, according to Curt Freed (University Of Colorado School of Medicine, CO, USA).

He notes, for example, that there was a high tumour rate (20%) among the grafted animals, which occurred after only a few weeks of follow-up. “For a human application, the FDA [US Food and Drug Administration] would probably insist on zero tumours for at least one year after transplant into a large number of subjects. That level of protection will only come from cells that have been permanently differentiated in vitro.”

Nevertheless, Freed says that the use of embryonic stem cells for Parkinson's disease has great therapeutic potential. “If differentiation of human embryonic stem cells to dopamine neurons can be successfully performed in tissue culture, with no residual embryonic stem cells, this strategy could provide a safe source of dopamine neurons for transplantation into patients with Parkinson's disease.”

Thomas S May

Does copper have a role in ALS?

Neuronal damage in familial amyotrophic lateral sclerosis (ALS) may not be copper dependent after all, according to research done by Philip Wong and colleagues (Johns Hopkins University School of Medicine, Baltimore, Maryland, USA). “ALS researchers will sit up and pay attention to these new findings by Wong and his colleagues. This is going to force the field to rethink ALS”, says Harry Orr (University of Minnesota Medical School, Minneapolis, MN, USA).

Up to 10% of cases of ALS are familial. About 25% of these familial ALS cases are linked to a mutation in the superoxide dismutase (SOD1) gene. Since SOD1 contains copper, researchers have long considered copper to be implicated in the motor-neuron degeneration seen in ALS. Indeed, previous work done in vitro supported a role for copper in the pathophysiology of the disease.

Wong's results, however, which used a genetically-modified mouse model of familial ALS, suggest that the neuronal damage may not be copper-dependent but rather that a lethal function unrelated to the normal protective antioxidant role of SOD1 is a more likely cause of cell death.

In their experiments, Wong and colleagues built a second defect into a commonly-used mouse model of familial ALS. For copper to reach its intracellular target protein (in this case SOD1), it needs a carrier called a “copper chaperone”. When the copper chaperone was inactivated in the genetically-modified mice, the researchers found that although the amount of copper-loaded mutant SOD1 was reduced, disease symptoms remained.

These data will “focus research toward other possible mechanisms involved in the cause of ALS”, says

Wong. “This experiment will hopefully solidify in other researchers' minds that we need to concentrate on alternative theories.” However, Wong admits that uncovering the mechanism by which mutation of SOD1 causes ALS remains a complex and challenging problem. The answer may lie within the mitochondria, or in the protein aggregates seen in motor neurons in ALS. Protein aggregates exist in other neurological disorders like Huntington's, Parkinson's, and Alzheimer's. “A second gene could be involved, too”, says Wong, “that intercepts with the SOD1, or another pathway, to affect motor neuron degeneration. We've learned from the Alzheimer's field that different genes converge into one common biochemical pathway to cause pathology. Similar events could be occurring in ALS.”

Elaine A Richman