Xenotransplanting Neural Cells

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Clinical xenotransplantation is currently being tested in the treatment of central nervous system disorders. Localization of cell death or dysfunction to specific sites allows the lesions to be treated by cell transplantation. Partial reversal of neuronal deficits in the CNS could be brought about by rebuilding of circuitry and neurotransmitter release or by secretion of trophic factors. For neural cell transplantation to be effective by any of these mechanisms, the cells must be able to form connections with host neural circuits, or donor neurotransmitters and trophic factors must be recognized by receptors on cells of the host.

Animal Studies

Studies in animals have clearly shown that when fetal neurons from disparate species are used to reconstruct neural circuitry, signals for neural development are sufficiently conserved to allow repair across species combinations. The host brain is apparently permissive for the extension of xenogeneic axons and the formation of synapses.[1] Studies in a number of models, including Parkinson's disease, demyelinating diseases, spinal cord lesions and stroke[2] indicate that circuits can be reestablished with neural xenografts. The capacity for correct growth of neural processes in the CNS after degeneration or damage is remarkable in a tissue that was once thought to be incapable of repair. These conclusions open the way for therapies that could reconstruct pathways lost to neurodegenerative disease or trauma-induced lesions.

Clinical Studies

In the clinical studies published to date, these observations have appeared to hold for porcine neural grafts in humans. In recently published work,[3] 12 patients who had been transplanted with porcine fetal cells were clinically monitored for one year. These data showed that the porcine fetal neurons could be transplanted safely and resulted in improvements in the united Parkinson's disease rating scale (UPDRS) when the patient was not on medication for his Parkinson's disease. One of the patients who died because of a pulmonary embolus provided an opportunity to assess the survival of porcine neurons 7.5 months after transplantation.[4] Examination of the striatum from this patient revealed that the porcine neural cells had survived in the CNS and had extended processes into the host brain.[4] Tyrosine hydroxylase positive neurons were present, indicating that dopamine-secreting cells had survived in the porcine xenograft. No evidence for rejection of the graft was observed in the histological analysis: expression of MHC class II was low in the graft as well as the surrounding host tissue, and staining for T cells with anti-CD3 antibody was minimal, indicating that few lymphocytes were infiltrating the graft. Results from these studies provide the first evidence of long-term survival of xenografts in patients and indicate that these cells can provide benefit to patients with neurodegenerative diseases.

These results are similar to those reported for a series of patients in Sweden transplanted with tissue from human fetal brain. Human fetal tissue from the ventral mesencephalon transplanted into Parkinson's patients replaces lost dopaminergic neurons and improves motor function, bradykinesia, and rigidity.[5] The transplanted cells reinnervate the striatum where they display normal electrical properties and secrete dopamine.[5] Significant side effects of the transplantation were not observed. Others have demonstrated survival of dopamine-producing neurons 18 months after transplantation in the allogeneic system.[6] These results correlate with

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PET scanning data that show uptake of fluorodopa by (transplanted) dopaminergic neurons in the striatum of these patients.

In the porcine-to-human xenograft studies, we are near completion of a phase 2 clinical trial in Parkinson's patients who received placebo or cell transplants. Clinical trials in focal epilepsy and stroke have been initiated and the preliminary findings suggest the occurrence of clinical improvements. Such trials will provide new information on the efficacy of xenografts for nervous system disorders.

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Immunology of Neural Xenografts

Both the environment for the xenograft in the host and the nature of the donor tissue account for the absence of rejection of these grafts. Neural cells are more resistant to rejection than cells from other organs. In fact, cotransplantation of nonneuronal cells has been shown to exacerbate rejection, and immunosuppressants that block upregulation of MHC antigens in transplanted chromaffin cells do not protect endothelial cells from the same species.[7] The grafts may resist rejection due to the lack of donor vascular endothelium which is the primary site for natural antibody binding to organs. Their low expression of histocompatibility antigens and other molecules involved in immune recognition may partially account for their survival in the host. But the environment of the CNS is also an advantage for the survival of the cells. Transplantation within the CNS is often accomplished without use of immunosuppression. Tight junctions between brain capillary endothelial cells that constitute the blood-brain barrier and a lack of lymphatic drainage prevent entry of lymphocytes and antibodies as well as trafficking of dendritic cells to lymph nodes for amplification of an immune response. Low expression of MHC class I and class II antigens suggests a dearth of antigen-presenting cells in the brain environment. Furthermore, once an activated T cell crosses the blood brain barrier and encounters antigen, the cytokines that regulate the immune response favor survival of the graft. Immune responses in the CNS are mediated by T cells that are prone to Th2 cytokine production.[8] In fact, astrocyte-mediated antigen presentation results in the secretion of Th2 cytokines by T cells and poor production of Th1 cytokines. Resident microglia may arrest immune responses in the CNS by eliciting T cell death after activation.[9] However, immune privilege is not complete and a need for immunosuppression to prevent graft rejection has generally been observed when species barriers are crossed.

Preformed antibodies are a major problem for xenotransplantation outside the CNS, and antibodies in humans that react with determinants on the cell surface of lower mammalian species are one barrier that prevents successful xenotransplantation in humans. The antibodies are directed primarily against an alpha-linked galactose determinant. Antibody-mediated rejection of xenografts is less of a problem in the CNS than in the periphery. It appears that antibodies can play a role in rejection of neural xenografts in animals, but in the case of porcine fetal neural grafts in the patients treated so far, rejection due to the presence of these antibodies has not been observed.

These immunological factors appear to account for the successful application of neural transplantation in humans and have allowed us to study the innervation of host neurons by neurons from other species. The success of the work in animals has suggested that this therapy could be applied in humans and these studies are now yielding insights into the safety and potential benefit of neural transplantation in patients with neurodegenerative disease or CNS lesions.

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