

Scientific Updates

Research news and notes

1. Mechanism of neuroprotection by adipose stromal cells

A recent article in *Neuroscience Letters* [7] revisits the neuroprotective effect of adipose tissue stromal/stem cells (ASC) on neural tissue damage. These cells do not differentiate into neurons and probably act through paracrine mechanisms. To study the effect of factors secreted by ASC, the authors incubated cerebellar granule neurons with and without medium in which ASC were previously immersed (ASC-conditioned medium [ASC-CM]). Neuron apoptosis was induced by serum and potassium deprivation, and ASC-CM protected against apoptosis in this system. Next, the authors neutralized likely neurotrophic factors present in ASC-CM one by one and found that Insulin-like Growth Factor-1 was the most important for neuroprotective activity. This study proposes a mechanistic basis for the effect of adipose stromal cells on neuronal survival and raises important questions. Could transplantation of adipose stem cells be a promising paradigm to alleviate neural tissue damage? Adipose stromal cells can be obtained from the patient with relatively low surgical risk and obviate the problem of allograft rejection. Would the omentum be a good source? I remember seeing omental transpositions performed for cerebral ischemia and anecdotal evidence for efficacy [3,6]. Is it time to revisit omental grafts for cerebral ischemia?

2. Functional integration of a neural graft in an experimental stroke model

Although neural transplantation may potentially improve functional outcomes in stroke and other disorders by various mechanisms, the ultimate goal is to provide a source of new cells that will actually integrate into the host circuits and repair the damaged brain. There are many obstacles to graft integration; they include issues of graft survival, graft differentiation, tumor formation, graft rejection, and other forms of hostile local environment. The tracking of the graft

is also not easy. In a recent study, Daadi et al [2] from Stanford used an approach that creates an optimized environment for engraftment in experimental stroke. They transplanted the cells in a syngeneic rat model, where compatibility is not an issue. Cells were taken from the median eminence (a temporary fetal periventricular structure that is rich in neural stem cells) of fetal rats that were carrying the green fluorescent protein gene, making it easy to track the grafted cells in the host. The recipient animals were syngeneic adult rats that did not express the fluorescent protein. The rats were subjected to a temporary occlusion of the middle cerebral artery. Two weeks after the stroke, the animals received grafts in 4 sites around the stroke, targeting the zone of partial injury adjacent to the area of complete infarction. This zone has structural integrity but is depleted of neurons. Controls received either vehicle or fibroblasts. Behavioral analysis at 4 weeks after transplantation showed reduced motor deficits in the rotarod and elevated body swing tests compared with controls. Under the microscope, the grafted median eminence cells (MEG) cells displayed differentiation into multiple neuronal subtypes, established synaptic contact with host cells, increased the expression of synaptic markers, and enhanced axonal reorganization in the injured area. Patch-clamp recording demonstrated that the MGE cells received postsynaptic currents from host cells—an initial demonstration of true reciprocal innervation and communication between the graft and recipient neurons and a sign of true integration.

This is a very important article as a proof of principle: a graft can survive and integrate into the host brain. The next challenge is to expand the paradigm to other situations—other species, and transplantation across immunological and even species barriers. This may prove a very difficult but probably worthy pursuit.

3. Neurologic outcome of long-term glioblastoma survivors

The prognosis for glioblastoma multiforme (GBM) patients remains dismal: 14 months median survival with best current treatment [1,5]—although it is improving and more patients experience long-term survival of 3 years or

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more [4]. Therefore, as intensive research continues into new therapies for GBM, Hottinger et al [4] from Sloan-Kettering decided to look into the clinical outcome of these long-term survivors. They reviewed the cases of 352 consecutive patients first seen at their center between 2001 and 2003. Thirty-nine (11%) were defined as long-term survivors of more than 3 years, and their characteristics as well as clinical outcomes were reviewed. Median survival was 9.15 years (range, 3-18 years). Median age was 47 years (range, 16-69). Nineteen of the patients each had either complete or subtotal resection, and only 1 had surgical intervention limited to a biopsy. All received focal radiotherapy with a median dose of 5940 cGy; 18% received concurrent temozolomide. Adjuvant chemotherapy was administered to 35 (90%). Twelve patients (31%) remained in continuous remission. Twenty-seven had tumor progression with a median of 29.2 months after diagnosis (range, 1.2-167 months); 18 had multiple relapses. Median Karnofsky Performance Status at last follow-up was 70; 85% of long-term survivors had at least 1 significant neurologic deficit. Radiation necrosis, radiation-induced leukoencephalopathy, and strokes each occurred in about a quarter of the patients. Treatment-related complications occurred a median of 2.7 years from diagnosis (range, 0.9-11.5 years).

This is an important article. We witness a continuing effort to improve the outcome of patients with GBM. This article reminds us that outcome is not only about survival but also about function. The authors provide an excellent report of the neurologic condition of the long-term survivors. It is interesting to note that only a few of the long-term survivors were in remission; for many, extended survival was the result of repeated treatment for recurrence. Longer survival also allowed the delayed effects of the treatment to assert themselves. The current treatment paradigm was developed

for a disease where long-term survivors are rare, and delayed deficits are acceptable when the alternative is certain early death. A study of functional outcomes must be repeated periodically to make sure that new treatments result in better outcomes, not just increased survival.

Ben Roitberg, MD
 Department of Surgery
 Section of Neurosurgery
 University of Chicago
 Chicago, IL 60637, USA
 E-mail address: roitbergb@gmail.com

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