Regenerative Medicine: Reprogramming Fibroblasts to Make Stem Cells

Replacing cells after stroke makes sense. Many cell types including neurons are lost. As the common final pathway of electrical and chemical signaling in the brain, neurons should be replaced to optimally reduce disability and handicaps. Critical and as yet unanswered questions are only beginning to be addressed: Which cells do we transplant? When do we transplant them? and Where do we transplant them? The most exciting new piece of data in 2007 comes from studies at MIT. The University of Wisconsin and Japan that suggest that fibroblasts can be reprogrammed to make embryonic stem cells; (2) they offer a strategy to be addressed: Which cells do we transplant? When do we transplant them? and Where do we transplant them? The most exciting new piece of data in 2007 comes from studies at MIT. The University of Wisconsin and Japan that suggest that fibroblasts can be reprogrammed to make embryonic stem cells; (2) they offer a strategy that embryos need not be destroyed to generate stem cells; (3) they offer a strategy that embryos need not be destroyed to generate stem cells; (3) they offer a strategy for developing embryonic stem cells that are genetically identical to their recipient. This feature overcomes issues of rejection and supply that plague both embryonic and adult stem cells; (3) they offer the opportunity to study in a dish via culturing and reprogramming fibroblasts from high risk patients the mechanisms that confer susceptibility of genetically high risk individuals to stroke.

Giving the Brain a Push: Epo, SDF-1, Angiogenesis and Beyond

A parallel approach that has garnered significant attention in 2007 and that is closer to human testing involves the use of growth factors or drugs to increase production of neural progenitors in the subventricular zone of the brain after stroke. A number of distinct growth factors can increase neurogenesis in central nervous system germinal zones after injury: erythropoietin, stromal cell-derived factor-1 (SDF-1), and granulocyte colony stimulating factor. Increased neurogenesis must be coupled with a strategy that permits recruitment of these “repair” cells to the site of injury. Chemokine receptor-4 is a receptor on progenitor cells that when bound with a gradient of SDF-1 facilitates homing of progenitors to injury sites. The precise regulators of SDF-1 in injured brain remains unclear, but elegant studies from Carmichael and coworkers suggest that SDF-1 is released by regenerating blood vessels and provides a source of chemotactic growth factor to facilitate survival and migration of neural progenitors. De novo angiogenesis is regulated by vascular endothelial growth factor. Recent studies indicate that Epo, vascular endothelial growth factor and SDF-1 are transcriptionally regulated by hypoxia via the transcriptional activator hypoxia-inducible factor 1. These findings suggest that neurogenesis, angiogenesis and chemotaxis of new born neurons into the injury site can be potentially regulated by a drug that stabilized hypoxia-inducible factor 1. Indeed, studies from a number of groups have identified small molecule activators of the hypoxia-inducible factor pathway that are ripe for testing in this context. Some of these drugs are already in phase II human clinical trials for other diseases and could be tested in preclinical recovery studies within the year.

Genetic Modifiers of Plasticity May Pave the Way to Novel Strategies for Rehabilitation

Recent studies suggest that forced use or robotic training can facilitate motor recovery and change motor map topography. The relevant insight is that fundamental principles underlying neural plasticity may offer a molecular roadmap for therapeutics. Kleim and Cramer published a potentially ground-breaking study demonstrating that polymorphisms in the gene for the growth factor, BDNF (val66met) are associated with smaller increases in the amplitude of motor-evoked potentials and motor map reorganization. These studies suggest an important role for BDNF in human plasticity. Given the prevalence of this mutation in distinct ethnic groups, the findings also predict that those with a val66met mutation will...
recover more poorly after stroke rehabilitation. These exciting hypotheses are currently being evaluated in animals and humans. Affirmation that the val66met mutation reduces efficacy of motor rehabilitation would ignite a search for drugs that overcome the BDNF secretion defect associated with this mutation.

**Imaging in Rehabilitation**

A major advance in stroke rehabilitation research this year has been the increasing use of noninvasive imaging techniques such as functional MRI, electroencephalography, magnetoencephalography and transcranial magnetic stimulation to facilitate the development of therapeutic interventions that are underpinned in the neurobiology of adaptive changes in the human brain.8

Although the benefits of early therapy are universally acknowledged, it is only recently that a functional MRI study has shown that cerebral activity to passive movements is reduced significantly in stroke patients and decreases further with time in the absence of activity.9 On the other hand, daily training for 4 weeks with repetitive passive and active arm movements increased cortical activation significantly. This suggests that there is a progressive downregulation of sensorimotor activity with inactivity in stroke patients, which is reversed by training. Another study suggested that it may be possible to upregulate sensorimotor activation further by using the conditioning effects of repetitive peripheral magnetic stimulation to enhance recovery.10 Cortical level positron emission tomography showed significantly increased activation of the parieto-premotor network in response to increased proprioceptive inflow from painless muscle contractions elicited by repetitive peripheral magnetic stimulation which was associated with improved kinematics of finger movements and reduced spasticity. This gives rise to the possibility that such techniques can complement existing therapy inputs to enhance recovery in stroke patients.

It has always been difficult to determine when a stroke patient has reached their full potential for recovery. Most clinical and imaging techniques used to identify this potential have their limitations, and prognostication remains an inexact and sometimes expensive science. Estimation of the functional capacity to recovery is particularly important for chronic stroke patients, especially as a recent meta-analysis of functional imaging studies for intervention effects in stroke rehabilitation has shown that clinical improvements occurred even late after injury and after subjects were deemed to have reached a recovery plateau.11 More importantly, this clinical improvement was accompanied by cortical reorganization that depended on the type of intervention given. The identification of such patients was the subject of a recent study, in which transcranial magnetic stimulation and MRI were used in conjunction to predicted functional recovery potential.12 The study showed that transcranial magnetic stimulation and functional MRI complement each other in determining the integrity of corticospinal tracts, essential for recovery. A potential for improvement up to 3 years after stroke was associated with the presence of motor-evoked potentials to transcranial magnetic stimulation in the affected limb and asymmetry in fractional anisotropy of the internal capsule of less than 0.25. The benefits of treatment declined with time and increasing disruption of the corticospinal tracts. The implication was that it may be possible to develop algorithms for patient selection to increase the positive yield of both research studies and clinical programs using specialized or novel interventions.

Advanced imaging studies have also provided new insights into the rehabilitation of neglect. A recent study has shown that breakdown of functional connectivity in ventral frontoparietal networks, known to be associated with nonspatial attention, underlies behavioral deficits in spatial neglect.13 Furthermore, the study showed that nonspatial attention training was associated with improvements in neglect underpinned by changes in cortical activation patterns in these or other areas known to be associated with attention, suggesting that new cortical subcortical connections may be formed to overcome this impairment. It is well-known but less recognized that neglect may be associated with motor impairments. Many patients with neglect have directional hypokinesia and are slower to initiate a motor response to targets appearing in the left hemispace, even when using their unaffected arm. The precise anatomical location of this impairment is debated, but a recent article has localized these motor deficits associated with neglect to the basal ganglia, suggesting that a relative depletion of dopamine in the nigrostriatal pathway on the same side of the lesion may be an important pathophysiologic mechanism and potentially amenable to intervention.14 A meta-analysis of magnetic resonance perfusion imaging studies in neglect patients has shown that hypoperfusion of the right angular and/or the superior temporal gyrus may be an important cause of neglect.15 Furthermore, fluctuations in neglect in the acute-subacute period after stroke are often due to changes in blood flow caused by changes in blood pressure, emphasizing the importance of vascular assessments and appropriate management to ameliorate such impairments during rehabilitation.

**Novel Interventions**

Several small clinical therapy studies on novel interventions were published last year that either challenged existing practices or investigated new emerging techniques. Although their findings are of interest, many lack validity because of small sample sizes or methodological limitations. Repetitive transcranial magnetic stimulation used as adjuvant to constraint-induced therapy for upper-limb hemiparesis had little effect on motor learning in a group of stroke survivors over and above constraint-induced therapy.16 On the other hand, motor imagery training combined with a conventional stroke rehabilitation program significantly enhanced lower-extremity motor recovery and motor functioning in subacute stroke patients.17 An electric stimulator to contract the paretic hand extensor muscles thereby open the hand in chronic stroke patients applied for 3 hours a week for 6 weeks was associated with a significant increase in maximum voluntary finger extension, finger-movement control, and box and block test score at 1 and 3 months after treatment.18 The benefits of cognitive training for memory deficits in stroke were assessed in 2 studies consisting of 18 patients in all. A formal meta-analysis could not be performed, but neither
study nor their pooled data showed any significant effect of memory rehabilitation on performance of objective memory tests or on subjective measures of memory. Clearly these areas need further exploration in future research.

Religious Beliefs and Stroke Rehabilitation

An interesting development in rehabilitation research this year is the increasing number of studies investigating the relationship between spirituality, faith and outcomes of rehabilitation in stroke patients. A review of existing research on these relationships concluded that religion and spirituality were linked to positive physical and mental health outcomes in individuals with disabilities because religion was used by many to help them adjust to their impairments and to give new meaning to their lives. The role of religion and spirituality as important coping strategies was investigated systematically in a well characterized sample of acute stroke patients using objective measures of outcome. This randomized controlled trial showed that although people with religious beliefs experienced the same amount of stress as those who did not have these beliefs, they were able to deal better with negative life events and the attendant stress. Another well designed observational study examined the association between attendance at religious services and change in physical functioning over 3 years in older Mexican American stroke patients with residual disability. The study showed that frequent attendees at religious services before stroke had significantly less decline in activities of daily living compared with infrequent attendees, even after controlling for demographics, medical conditions, health behaviors, and physical mobility. Hence, it would appear that spirituality or religiosity itself may not reduce emotional distress after stroke, but people who generally are religious have better abilities to cope with chronic illness. As stroke rehabilitation includes not only restitution of physical or functional limitations but also the management of psychological and social sequelae that affect long-term adjustment, the positive effects of spirituality and religious beliefs merit further investigation.

And Finally . . .

The gulf between what is known and what is done in stroke rehabilitation is best illustrated by a clinical study from Canada earlier this year. Urinary incontinence is a common, distressing, well known and frequently ignored problem in stroke rehabilitation, despite evidence to support early recognition and management. In a sample of 663 Occupational Therapists and 656 Physiotherapists working in stroke rehabilitation, only 40% identified urinary incontinence as a problem, fewer than 20% used best-practice assessments, and less than 3% used best-practice interventions. It is likely that these data will be replicated in most settings and across professions, highlighting the need to translate what we read in journals to our day to day clinical practice.

Disclosures

None.

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