Orchestrating Recovery: Cell-based Therapy for Stroke

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Received: 29 June 2011 / Accepted: 29 June 2011 / Published online: 9 July 2011
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How does cell therapy for stroke differ from the host of therapies that have been investigated with utter failure for the past decades? Why work with cells as a means to provide therapeutic relief for stroke? To address these questions, we must peer into the mechanisms of action of cell therapy for stroke and distinguish it from neuroprotective drug-based therapies.

Initially, the overwhelming conceptual approach for mechanisms of action for cell therapy for stroke and neurological disease was that cells replace dead tissue. “Stem cells” become neurons and integrate into the complex and elegant architecture of the injured brain to replace neurons and parenchymal cells sent to their death by the vascular insult. Although, by functional definition, stem cells can differentiate and become neural cells, reviewing the great mass of experimental data showing that the paucity of cells that enter the adult brain could not, by any means, replace the millions of brain cells lost after the induction of a malignant stroke in animals, kills this argument of replacement therapy. In addition, for the vast majority of cell types employed, many of them were not stem cells but adult progenitor cells and others, and the obvious absence of data showing evident replacement and quasi miraculous rebuilding of the devastated brain tissue after the cataclysmic infarct clearly devastates a replacement hypothesis for cell-based therapies for cerebral infarction for the vast majority of cells used to treat stroke.

With the preponderance of evidence demonstrating that cell-based therapies function not as a brick in the building

of the brain, we can begin to truly appreciate the functional elegance of injecting a living therapy, a cell that senses and responds to and alters the cerebral microenvironment to stimulate neurological recovery. Cell-based therapies, whether the cells are embryonic, adult progenitor, and IPS cells, actively negotiate and gauge the needs of the tissue to stimulate multiple multifaceted restorative processes. The exogenously administered cells generate a variety of restorative trophic factors and proteases, and induce signal transduction pathways titrated to the conditions of the cerebral microenvironment and thereby provide a poly-pharmacy tuned into the needs of affected cerebral tissue. Likely more importantly, cells stimulate within the parenchymal and vascular cells, e.g., astrocytes, microglia, and endothelial cells, the production of factors that remodel the central nervous system (CNS) to compensate for the stroke-induced destruction of tissue. Thus, the administered cells orchestrate recovery by recruiting and stimulating parenchymal cells to initiate restorative coupled processes, which include angiogenesis, neurogenesis, oligodendrogenesis, remyelination, and synaptogenesis. In addition, the exogenously administered cells may modulate the immune system and cytokines to harmonize with the induced restorative processes. Essentially, the point of cell-based therapies for the treatment of stroke is that the living cell, by its distinct ability to probe and to sensitively stimulate endogenous restorative processes within the organism, promotes neurological recovery.

Whether cells are directly delivered to the brain by intraparenchymal injection or indirectly via a vascular, venous or arterial, route of administration, cell-therapy enhances neurological recovery. These various routes of cell administration support the multifaceted stimulation and amplification of endogenous restorative processes. Direct administration, bypassing the issue of body-wide cell distribution, likely provides benefit by direct cell interaction

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with endogenous brain and vascular cells and the release and stimulation of restorative factors. A vascular route of administration allows for the contribution of systemic responses to the treatment, which incorporate more generalized immune response and possible production of factors in other organs, e.g., lung and liver, which may contribute to recovery. The vascular route of administration may also promote an interaction of exogenously administered cells with the luminal vascular wall which stimulates angiogenesis/arteriogenesis and the vascular generation of factors which protect the microvasculature and transform them into restorative “factories”.

Returning to the central questions noted above. Cell-based therapy, designed as a restorative treatment for stroke, primarily treats the intact brain. In sharp contrast, the traditional pharmacological neuroprotective therapies treat the lesion, attempting to reduce the volume of cerebral infarction. Treating the lesion with a drug, one is greatly constrained by the race against time to salvage dying cells and forestalling necrotic and apoptotic processes, and by delivery issues, given the reduced and sometimes negligible tissue perfusion which compromises the delivery of salvaging drug. Restorative therapy with cells, in marked contrast, has a much extended therapeutic window, weeks if not longer post stroke, and tissue perfusion to deliver cells, is not an issue, with adequate if not enhanced perfusion in the lesion boundary and other regions of the

CNS. Cells are also “smart”; they respond to the microenvironment and modulate their expression of factors and stimulate parenchymal cells based on the degree of injury. In contrast to pharmacological therapies which are designed to target a specific pathway, cells, as living responsive systems, stimulate concurrent and parallel endogenous restorative molecular and physiological pathways.

This conceptual approach to the source of cell-based therapy does not exclude, in any way, the ability of exogenously administered cells to evoke neuroprotection. Cell-based therapies produce factors and stimulate parenchymal and vascular cells to reduce apoptosis and modulate the immune system to reduce volume of cerebral infarction under specific treatment protocols.

There is much work to be done in translating laboratory findings of the treatment of stroke with cell-based therapy to the clinic. However, what has been clearly demonstrated so far is that it is possible to activate, by means of this living treatment, endogenous restorative processes that reduce neurological impairment after a large cerebral infarction. Investigation of how exogenously administered cells talk to and manipulate the CNS and possibly the immune system to amplify endogenous restorative processes will likely yield information vital to the treatment of all neural injury and possibly neurodegenerative disease.