WILL STEM CELL THERAPY BECOME IMPORTANT IN STROKE REHABILITATION: NO?

Michael Chopp
USA

Stem cell therapy in general is based on the supposition that dead or injured tissue can be replaced by exogenously administered stem cells. This has been quite clearly demonstrated, particularly for treatment of stroke in the adult, to be a false premise. Exogenously administered cells, rarely undergo differentiation into parenchymal cells and integrate in substantial numbers into tissue. The quantity of cells administered also represents a miniscule number of the cells that need to be replaced. Cell-based therapies for the treatment of stroke, neural injury and neurodegenerative diseases are essentially catalysts that enhance endogenous restorative mechanisms within the organism. After stroke, the administered cells promote neurovascular remodeling and CNS plasticity by multiple mechanisms including paracrine mechanisms which stimulate parenchymal cells, primarily astrocytes, to produce trophic factors which enhance neurological recovery. There are multiple other means to stimulate neurorestorative processes, both pharmacological approaches as well as molecular possibilities. Thus, it may not be necessary to employ stem cells to promote the biological substrates of plasticity and neurovascular remodeling needed for recovery. Pharmacological approaches to be considered for inducing neurovascular remodeling and plasticity may involve means to reduce the generation of inhibitory glycoproteins by astrocytes to create a more permissive environment for sprouting. Astrocytes, as the most prevalent cell in the CNS, play pivotal roles in neurological recovery, and inhibition of astrocytic reactivity to stroke results in poor neurological recovery. Thus agents which stimulate astrocytic response may contribute to neurological recovery. In addition, agents which enhance, oligodendrogenesis to promote remyelination, neurogenesis, angiogenesis, and axonal and dendritic remodeling, may be coupled with rehabilitation to improve neurological recovery post stroke. Here, however, I want to focus on the stem cell, and we have demonstrated that it is not the stem cell but, the products of the stem cell that promote plasticity . Stem cells evoke neurological recovery by communicating with the parenchymal cells and other organs to reboot restorative processes. They do this by reinvigorating developmental programs, and upregulating the expression of developmental morphogens, such as sonic hedgehog. Activating the Shh expression of promotes the expression of transcription factors that impact expression of many genes. Among them, are tissue plasminogen activator, which promotes neurite outgrowth and rewiring of the cortical spinal track. Stem cells also stimulate parenchymal cell production of important factors such as VEGF and Angiopoietin which stimulate multiple pathways which promote recovery. As a means to identify ways to enhance the restorative effects of rehabilitation, it is important to investigate how stem cells communicate with the parenchymal cells and how they turn-on multiple pathways of neurorestoration. Stem cells send out nanoparticle lipid containers, called exosomes, which are absorbed by parenchymal and other cells. As cargo, these exosomes contain proteins, mRNA, RNA, lipids and microRNA. And it is the content of the exosomes, to a large extent the microRNAs that communicate instructions to parenchymal cells and to distant organs to initiate restorative processes. Thus, instead of using stem cells to treat neurological disease and stroke, it may be reasonable to employ the product of the stem cells, exosomes to amplify neurorestorative processes. Our data demonstrate that treatment of stroke, traumatic brain injury with the exosome product of stem cells enhance neurological recovery parallel to stem cell treatment. Thus, stem cells are not necessary agents to be used in concert with rehabilitation. There are other means, and possibly, the offspring of stem cells, exosomes containing essential genetic instructions for protein translational, may be a more viable approach than stem cells to be employed with rehabilitation for the treatment of stroke. The use of stem cells to stimulate plasticity to enhance recovery associated with rehabilitation also encounters risks. Stem cells, depending on their source, may stimulate teratoma. In addition, co morbid conditions such as diabetes, which affects nearly a third of all stroke patients may under certain conditions and treatment protocol, preclude the use of selective stem cell because of potential adverse effects. Recovery of neurological function post stroke is amplified by the interaction and synergy between rehabilitation and central nervous system plasticity. However, stem cell therapy may not be needed to enhance neurological function when coupled with rehabilitation.