Neurogenesis, Angiogenesis, and MRI Indices of Functional Recovery From Stroke

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Abstract—This article analyzes the mechanisms underlying the potentiation of functional recovery poststroke by cell-based and pharmacologic agents, which amplify endogenous neurogenesis in the subventricular zone and angiogenesis in the border of the ischemic lesion in the animal. Discussion of the interaction between angiogenesis and neurogenesis is provided and data are described demonstrating a role for matrix metalloproteinases expressed in perifocal vasculature as chemotactic for neuroblasts migrating from the subventricular zone. Monitoring angiogenesis and structural changes in the ischemic brain associated with functional recovery by means of MRI is described. We demonstrate that injured brain can be stimulated to promote angiogenesis and neurogenesis, which are coupled restorative processes that contribute to functional recovery from stroke and that MRI indices of these neurorestorative events are highly correlative with neurologic function and may be used in real-time monitoring of recovery from stroke. (Stroke. 2007;38[part 2]:827-831.)

Key Words: functional recovery • MRI

Fewer than 5% of stroke patients receive recombinant tissue plasminogen activator. Thus, there is a compelling need to develop treatments of ischemic stroke designed specifically to reduce neurologic deficits, which can target the vast majority of patients.

The injured brain after onset of stroke in the experimental animal is driven to a quas_developmental state exemplified by the induction of an array of genes and proteins last seen in the embryonic and developing brain. This observation suggests that injured brain is primed for potentiation of neurorestorative processes. There are multiple ways to promote these restorative processes, including cell-based and pharmacologic therapies. The cell-based therapies that are under intense investigation include bone marrow mesenchymal cells, cord blood cells, fetal cells, and embryonic cells among others. In addition, there are many agents that trigger endogenous neurorestorative processes within the brain that may contribute to the reduction of neurologic deficits after stroke.

Neurogenesis

In the experimental animal, stroke significantly increases the number of newly produced cells in the vicinity of the lateral ventricle and neurogenesis is present in the subventricular zone (SVZ) of patients with Huntington disease. A basic question is, what causes this amplification of neurogenesis in the SVZ? There are many molecular contenders for stimulating this process, including basic fibroblast growth factor, epidermal growth factor, insulin like growth factor 1, sonic hedgehog, and brain-derived neurotrophic factor. Increased production of new brain cells after stroke can also be attributed...
to a reduction in the G1 phase of the cell cycle. This reduction in cell cycle was associated with a reduction in expression of cyclic-dependent kinase inhibitors, including p27. The molecular primers for this increase in cyclic-dependent kinases are unknown. The observation of a stroke or cerebral injury-mediated increase in production of brain cells is also consistent with the concept that injured brain mimics an earlier stage of development.

Cell Migration—Doublecortin and Matrix Metalloproteinases

Doublecortin is a marker for migrating neuroblasts. Cells generated in the region of the lateral ventricle migrate long distances to tissue adjacent to an infarct. What allows these cells to bore through the ischemic tissue to sites distant from their birthplace and how do these cells survive their long distance travel? One factor that can facilitate the migration of neuroblasts to remote regions of tissue is that these cells produce matrix metalloproteinases (MMPs), particularly MMP 2 and MMPs degrade the extracellular matrix. Neuroblasts secreting MMPs can penetrate the continuum of the extracellular matrix and, like tumor cells, traverse a solid barrier to reside in the penumbral zone.

Migration of neuroblasts through the brain from the SVZ is unimpeded, and it appears that many cells survive the journey through regions of tissue alien from the birth source. We therefore asked the question whether these neuroblasts express proteins that are neuroprotective, proteins that facilitate the survival of these cells. Because doublecortin is a ubiquitous marker of migrating neuroblasts, we tested the hypothesis that doublecortin has a neuroprotective role in the migrating neuroblasts. SVZ cells derived from the rodent were subjected to oxygen glucose deprivation, mimicking some of the events after stroke. These cells show significantly increased expression of doublecortin. Cells transfected with the doublecortin gene also exhibited robust and significant increase in survival when subjected to oxygen and glucose deprivation. Likewise, siRNA, which reduced expression of endogenous doublecortin in SVZ cells, made the cells significantly more vulnerable to stress induced by oxygen glucose deprivation. Thus, these data indicate that doublecortin is not only a marker for migrating neuroblasts, but also insulates neuroblasts from the potential dangers of migration.

Neuroblast Migration and Vascular Signaling

In the normal uninjured rodent brain, neuroblasts are locked into a fixed migration pathway from the lateral ventricle to the olfactory bulb along the route of the rostral migratory stream. In sharp contrast, after stroke and injury, many cells deviate from this rigid path and migrate within the parenchyma to sites of injury. A fundamental question is, what are the molecular signals that dictate this rerouting to injured tissue? There is substantial literature demonstrating that chemokines, particularly stromal derived factor-1/CXCR4, contribute to the migration of these cells. CXCR4 is increased in neuroblasts, and stromal derived factor-1 is significantly increased in the cerebral tissue adjacent to the ischemic lesion. Do other factors target neuroblast migration? MMPs are strongly expressed, primarily in the microvasculature in the lesion boundary after stroke. We then asked the question, whether MMPs in the compromised vascular tissue adjacent to stroke also target neuroblasts to injured tissue? Using cell culture systems, we demonstrated that endothelial cells activated by a neurorestorative agent such as erythropoietin significantly increased the expression of MMP 2 and MMP 9 and significantly increased the migration of neuroblasts. MMP inhibitors greatly attenuated the endothelial cell mediated migration of neuroblasts. These data indicate that signals within the compromised microvasculature serve as a stimulus promoting neuroblast migration. In vivo data strongly support this hypothesis with the observations of expression of MMPs by the ischemic vasculature and the localization of migrating neuroblasts to this microvasculature.

MRI Monitoring of Plasticity and Recovery After Stroke

In the experimental animal, there are multiple interlaced neurorestorative processes activated after stroke and amplified with restorative treatment. These treatments revise brain architecture, including vascular changes associated with angiogenesis, neurogenesis, glial changes, reduction of scar tissue with treatment, increased presence of progenitor and mature oligodendrocytes after treatment, and changes in the white matter. Aspects of brain structural and angiogenic remodeling may be visible on MRI.

MRI Indices of Angiogenesis

Angiogenesis may contribute to recovery after stroke. Angiogenic vessels at early stages are permeable. We capitalize on this transient increase in vascular permeability and use it as a signal for new vessel formation. Vascular permeability can be quantified and detected using T1 indices of brain to blood transfer constants of extrinsic contrast agents such as gadolinium DTPA as well as intrinsic magnetization contrast methods and integrated multidimensional MRI techniques. In a recent study, we demonstrated that 1 to 2 weeks poststroke in the rodent treated with cell-based therapy, Ki, the transfer constant of Gd-DTPA was significantly and transiently increased in the penumbral region. The signals were not attributed to edema as indicated by T1/T2 images. Histologic measurement of vascular density.
We have reviewed some of our work addressing specific aspects in this restorative arena, demonstrating that the brain creates new neural cells in the adult similar to neurogenesis in the embryo; these neuroblasts express protective proteins, eg, doublecortin, and these neuroblasts respond to homing signals emerging from the vasculature in the injured tissue. The development of these restorative treatments and the amplification of brain plasticity are also being assisted by the use of noninvasive MRI indices of angiogenesis and structural anisotropy.

Appendix

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Disclosures

None.

References

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