Replacing Neocortical Neurons after Stroke

Fifteen years ago, a research report claiming that brain injury stimulates production of new neurons in postnatal mammalian forebrain would have been met with widespread skepticism. Since then, considerable experimental evidence has emerged indicating that neural stem cells and neurogenesis persist in specific regions of the neonatal and adult mammalian forebrain (reviewed in Ming and Song[1]). Many investigators now focus on analysis of the properties, regulation, and functional impact of neural stem and progenitor cells in the central nervous system.

The persistence of neurogenesis throughout life raises the possibility that the brain mounts an intrinsic regenerative response to replace neurons lost after stroke or other insults. Indeed, work in adult rodent stroke models over the past 5 years indicates that focal ischemic injury increases cell proliferation and neurogenesis in the forebrain subventricular zone (SVZ), the predominant germinative zone in the adult mammalian brain (see Lichtenwalner and Parent[2] for review). Stroke-induced neurogenesis is augmented by growth factor infusion and other manipulations.[3–7] Neuroblasts derived from SVZ progenitors, moreover, appear to be diverted to the injured striatum or hippocampus after ischemic injury to form medium spiny neurons or pyramidal cells, respectively.[5,8,9] This potential regenerative response to stroke is long-lasting[10] and occurs even in aged rodents.[11,12] A recent study of autopsy material from stroke patients suggests that neurogenesis in the adult human forebrain SVZ also is stimulated by ischemic injury.[13]

Findings that neocortical neurons are replaced after experimental stroke in the adult are controversial because unequivocal evidence is lacking. The functional consequences of stroke-induced neurogenesis also remain uncertain. Many newborn neurons generated after focal ischemia in the adult fail to survive,[8] and evidence to date that the remaining cells integrate and restore function is scarce. The recent development of animal models that allow specific depletion of neural progenitors should soon provide insight into some of these issues.

Because postnatal neurogenesis peaks in the first few weeks of life,[14,15] several groups have examined neonatal rodent models of hypoxic-ischemic (HI) injury, seeking a more robust forebrain neurogenic response. Although initial studies found stroke-induced SVZ neurogenesis in this setting, it surprisingly was short-lived and more modest in the neonate than had been found in adult stroke models.[16–18] Similar to results in the adult, no neocortical neurogenesis was found. However, a recent study in a chronic hypoxia model in neonatal mice[19] did provide evidence of cortical neurogenesis.

Yang and colleagues'[20] report in this issue of *Annals of Neurology* gives further impetus for optimism regarding self-repair prospects after neonatal brain injury. Using a well-characterized model of HI in neonatal rat, this group found a marked stimulation of SVZ neurogenesis and substantial numbers of new neurons in both striatum and neocortex after focal ischemic injury. These authors injected retroviral reporters into the striatal SVZ to show that many of the newborn neurons arise from the SVZ and migrate to injury.

The neurogenic response to neonatal HI was long-lived as some neurons generated after stroke persisted for several months. The numbers of surviving neocortical neurons, however, was small compared with the extent of neuronal injury and the large number of immature neurons observed initially. The authors, moreover, found no newly generated pyramidal neurons in neocortex. Only small, calretinin-immunoreactive, putative interneurons were identified as arising from progenitors after HI. This finding may reflect a fixed intrinsic programming of the SVZ neuronal progenitors, which derive from the ganglionic eminences in the embryo that generate interneurons in the neocortex and olfactory bulb, some striatal projection neurons, but no neocortical pyramidal cells.[21–23]

Although Yang and colleagues[20] suggest that their findings provide evidence that a more robust regenerative response exists in the injured neonatal cortex than in the adult, this conclusion appears to be premature. Many methodological factors could contribute to the different findings obtained in this study of neonatal brain injury versus studies in adult rodent brain injury models. The anatomic distribution and severity of tissue injury, the genetic background of the animals, the timing of bromodeoxyuridine administration, the timing of outcome analysis, and the rigor of the search for newly generated neurons are all critical variables that greatly influence experimental results. Patterns of brain injury, moreover, are not strictly comparable in neonatal and adult rodent stroke models. From a clinical perspective, the frequent occurrence of poor neurodevelopmental outcomes in neonates who have incurred hypoxic-ischemic brain injury[24] belies the putative resilience of the neonatal brain.

Several other important themes emerge from the results of this study. As has been reported previously in other forebrain regions,[25] the injured neonatal cortex favored survival of new oligodendroglia and astrocytes. Whether the functional impact of these new glia is beneficial or deleterious is unknown; however, the close anatomic relation observed between migrating

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neuroblasts and astrocytes suggests that gliogenesis strongly contributes to regenerative responses after brain injury. Another issue that Yang and colleagues[20] point out is that specific inflammatory mediators likely play pivotal regulatory roles in neurogenic and other regenerative responses. The potential trophic influence of certain inflammatory mediators therefore brings into question whether antiinflammatory therapy could inadvertently disrupt the reparative process.

The small numbers of newborn neocortical neurons generated after HI and lack of pyramidal neuron replacement in neocortex suggest that major challenges exist for stimulating repair from endogenous progenitors after stroke. Growth factor infusion or other manipulations to augment endogenous repair likely will be necessary. Optimal recovery from stroke or other brain insults, moreover, may require combining this approach with some types of neural stem cell transplantation to provide additional cell replacement or trophic support for endogenous progenitors.

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