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·Research Highlight·

Significant implications of Bcl-2 in the formation of striatonigral projection neurons in the ischemic striatum

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In adult mammals, including humans, the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone of the dentate gyrus (DG) show ongoing neurogenesis[1]. Cerebral ischemic insults trigger neurogenesis from neural stem cells or progenitor cells located in the SVZ and DG[2,3]. Newborn neurons are then functionally recruited into the circuitry of the CA1 region, striatum and DG granule cell layer[4-6].

The SVZ neural stem cell is a nestin- and glial fibrillary acidic protein (GFAP)-immunoreactive radial glia-like cell that probably arises from embryonic radial glia[7]. Although the SVZ neuroblasts are destined to migrate to the olfactory bulb *via* chain-like formations in the rostral migratory stream under physiological conditions, many migrate in chains toward the striatum after focal ischemia[4,8]. While the vasculature appears to play an important role in the migration of neuroblasts to regions of ischemic damage, several molecular factors including matrix metalloproteases and chemokine/chemokine receptor interactions may direct this ectopic migration to peri-infarct regions[9]. Importantly, the migration of SVZ neuroblasts to the injured striatum persists for up to a year after ischemia, suggesting that the SVZ may serve as a constant reservoir of new neurons that offers a long time window for therapeutic manipulations[9]. These findings raise the possibility of reparative potential of endogenous progenitors in the striatum for neurodegenerative disorders, including stroke. Unfortunately, however, most of the newborn neurons undergo programmed cell death in the injured striatum, and few differentiate into mature neurons, thus rendering the replacement of mature injured neurons inefficient[4,10,11].

Interestingly, work from Sun's lab showed that Bcl-2, an inhibitory regulator of apoptosis in the brain, enhances neurogenesis and prevents the apoptotic death of new neurons in the adult brain by inhibiting BMP-4 function *via* activation of β-catenin signaling[12,13]. These findings prompted them to examine whether Bcl-2 overexpression plays a role in the formation of newborn striatonigral projection neurons in the adult rat brain following a transient middle cerebral artery occlusion (MCAO). As reported in this issue of Neuroscience Bulletin, Guo *et al.*[14] stereotaxically delivered human Bcl-2-expressive plasmid (pBcl-2) into the ipsilateral lateral ventricle by microinjection to induce the overexpression of Bcl-2 protein in adult rat brains after MCAO, and fluorogold (FG), a retrograde tracer, was injected into the substantia nigra, a target of striatal projection neurons. One week after nigral microinjection, strong FG signals were detected in the substantia nigra and striatum as well as the pyramidal layer of the cerebral cortex in the hemisphere ipsilateral to the injection, but not in the contralateral hemisphere. These FG-positive cells were co-stained with NeuN, but not with GFAP, successfully tracing the striatonigral projection neurons.

The substantia nigra and striatum are the main compo-

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nents of the basal ganglia, which participates in a variety of brain functions including voluntary motor control, procedural learning, cognitive and emotional function. Within the basal ganglia, several neuronal projection pathways connect the nuclei, including the striatopallidal, striatonigral and nigrostriatal projection pathways. Previous work demonstrated that Bcl-2 accelerates the differentiation and maturity of newborn neurons in ischemic striatum at an early stage (2–4 weeks) of reperfusion after MCAO[12]. In the current work[14], Guo *et al.* found that pBcl-2 treatment increases the number of newborn neurons that were mature at 12 weeks of reperfusion. Most importantly, they observed that newborn neurons were further co-stained with FG at 12 weeks after ischemia, indicating that overexpression of Bcl-2 further promotes the formation of long projections from newborn striatal neurons to the substantia nigra.

More recently, a study from Sun's lab showed that the ischemia-induced newborn striatal neurons express glutamate NR2 and dopamine D2L receptors, which form the molecular basis for responding to inputs from cortical glutamatergic and nigral dopaminergic projection neurons[11], providing the first morphological evidence that newborn neurons in the striatum, a non-neurogenic region, can establish new striatonigral neural circuits, important pathways for the maintenance of motor function. Moreover, it is well known that expression of Bcl-2 in the central nervous system (CNS) neurons correlates with axon elongation in the developing brain, and deletion of the Bcl-2 gene reduces the ability of embryonic neurons to extend neurites in culture. In contrast, constitutive expression of Bcl-2 in postnatal CNS neurons reverses the loss of intrinsic growth capacity by CNS axons and leads to robust optic nerve regeneration in postnatal mice[15]. Together, these findings suggest that Bcl-2 plays a beneficial role in neurite growth in the adult brain. Thus, up-regulating Bcl-2 in the ischemic striatum may be a potential strategy for promoting the reestablishment of neural networks and the ability of brain repair after ischemic injury.

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