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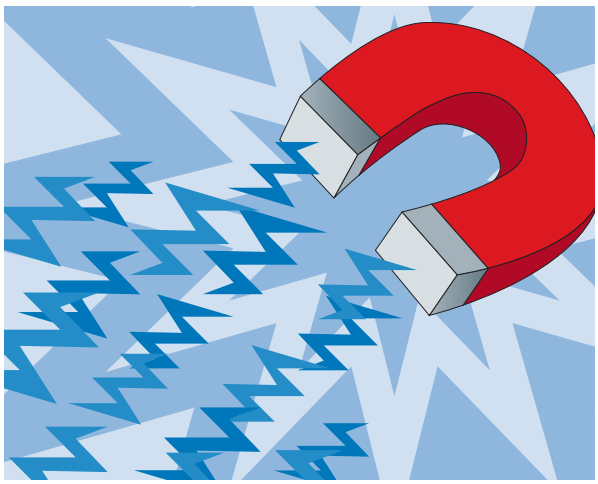
REPAIR

Long-distance attraction



Rodent models have shown that after stroke, new neurons are born in the subventricular zone (SVZ) of the brain and migrate to the degenerating striatum. Long-distance migration to the cortex can also occur, but what triggers neuroblasts to migrate there? Ohab *et al.* report that newly formed blood vessels around the injured cortex produce factors that attract migrating neurons, which then settle adjacent to those vessels in a neurovascular 'niche'.

The researchers produced focal strokes in mice in such a way that only the motor and somatosensory cortices were damaged. Immunohistochemical analysis of brain sections showed that neurons containing doublecortin (DCX, a marker for migrating or immature neurons in the adult brain) appeared first in subcortical white matter and then in the cortex surrounding the infarct site.

To determine whether these neuroblasts originated in the SVZ, the researchers injected this area at the time of the stroke with BrdU or with a lentivirus expressing green fluorescent protein (GFP) to label potential migrating cells. A week later, BrdU-labelled DCX-positive cells were found in both the subcortical white matter and in the peri-infarct cortex. This second region contained GFP-labelled DCX-positive cells 7 and 14 days after injection. These findings indicated that the labelled cells had indeed migrated from the SVZ to the cortex.

The neuroblasts ended up adjacent to and ensheathing vascular endothelial cells. Specifically, DCX-positive cells were found near blood vessels so recently developed that blood flow had not yet begun, demonstrating that neuroblasts had migrated to areas of post-stroke vascular remodelling. Indeed, blocking post-stroke angiogenesis with endostatin reduced the number of DCX-positive cells by tenfold.

But what was it about these newly formed blood vessels that attracted neuroblasts? Two candidate substances are the vascular growth factor ANG1 and the chemokine SDF1, the expression of which is upregulated by stroke. Indeed, ANG1 levels were increased along the entire path of neuroblast migration and SDF1 was upregulated throughout the infarct core. Conveniently, the neuroblasts that had migrated to these regions had receptors for ANG1 and SDF1.

To prove that the two factors indeed recruited neuroblasts, the researchers administered SDF1β or ANG1 systemically for 7 days post-stroke, which increased the number of neuroblasts clustered around blood vessels in the injured region. Conversely, blockade of the SDF1 or the ANG1 receptors resulted in abnormal migratory pathways. SDF1β and ANG1 infusion increased the initial migration of neuroblasts, although not their long-term survival, and improved behavioural recovery during the first 10 days after stroke, corresponding to the time in which neuroblasts are recruited.

Given the recent evidence that stroke-induced neurogenesis and possibly neuronal migration also take place in the human brain, these results provide interesting possible targets for treatments that are aimed at improving post-stroke neuronal recovery.

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ORIGINAL RESEARCH PAPER Ohab, J. J. *et al.* A neurovascular niche for neurogenesis after stroke. *J. Neurosci.* **26**, 13007–13016 (2006)

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