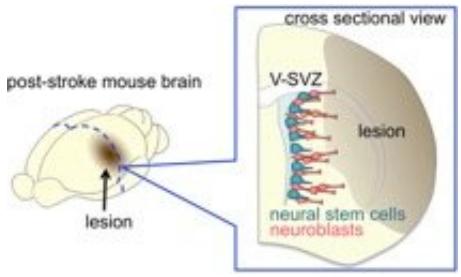
A new strategy for brain regeneration after stroke

December 12 2018



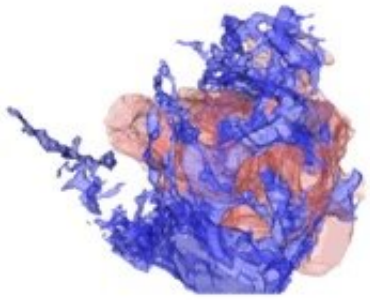
In a rodent ischemic stroke model induced by transiently blocking the middle cerebral artery, the most commonly affected vessel in human patients, some V-SVZ-derived neuroblasts migrate toward the lesion, where they mature and become integrated into the neuronal circuitry. Credit: Kazunobu Sawamoto

Stroke is a leading cause of death and chronic disability in adults, causing a heavy social and economic burden worldwide. However, no treatments exist to restore neuronal circuitry after a stroke. While most neurons are generated during embryonic brain development, new neurons continue to be produced in the ventricular-subventricular zone (V-SVZ) of the adult brain.

In rodent olfaction, immature new neurons called neuroblasts form chain-like aggregates that migrate to the olfactory bulb, where they differentiate into interneurons. However, in the case of brain injury, the mammalian brain has only a limited ability to regenerate neuronal circuits for functional recovery. In a rodent ischemic stroke model

induced by transiently blocking the middle cerebral artery, the most commonly affected vessel in human patients, some V-SVZ-derived neuroblasts migrate toward the lesion (Fig. 1), where they mature and become integrated into the neuronal circuitry. However, the number of these new neurons is insufficient to restore neuronal function.

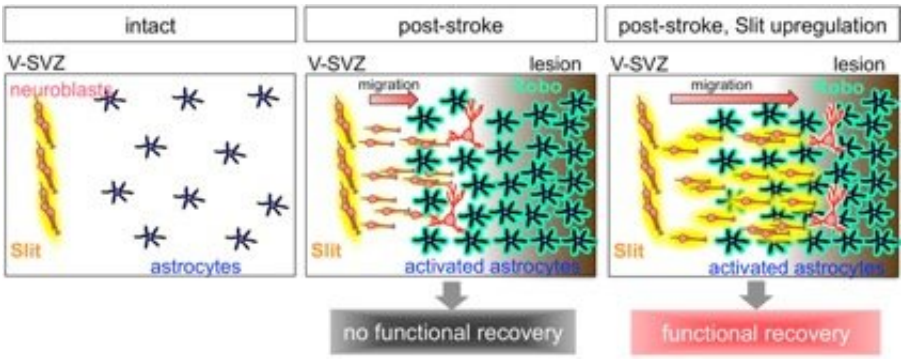
Dr. Kazunobu Sawamoto (Professor, Nagoya City University and NIPS) and Dr. Naoko Kaneko (Associate professor, Nagoya City University) in collaboration with Dr. Atsushi Nambu (Professor, NIPS) and Dr. Yasuo Kawaguchi (Professor, NIPS) have revealed a novel mechanism for neuronal regeneration, using the mouse model for ischemic stroke. Within a few days after stroke, astrocytes, a major population of macroglia, in and around the injured area become activated, exhibiting larger cell bodies, thicker processes, and proliferative behavior. The migrating neuroblasts must navigate through this astrocyte meshwork to reach the lesion. Using three-dimensional electron microscopy and live imaging, the research team demonstrated that neuroblast migration is restricted by the activated astrocytes in and around the lesion (Fig. 2).



Neuroblasts (red) migrate toward a lesion through a meshwork of processes from a single astrocyte (blue), as shown by 3D electron microscopy. Credit: Kazunobu Sawamoto

In normal, olfaction-related migration, neuroblasts secrete a protein called Slit, which binds to a receptor called Robo expressed on astrocytes. Slit alters the morphology of activated astrocytes at the site of neuroblast contact, to move the astrocyte surface away and clear the neuroblast's migratory path. However, in the case of brain injury, the migrating neuroblasts actually down-regulated their Slit production, crippling their ability to reach the lesion for functional regeneration. Notably, overproducing Slit in the neuroblasts enabled them to migrate closer to the lesion, where they matured and regenerated neuronal circuits, leading to functional recovery in the post-stroke mice (Fig. 3). These results suggest that strategies designed to help migrating neurons reach the lesion may improve stem/progenitor cell-based therapies for brain injury.

The study is published in *Science Advances*.



Left: Intact brain. Middle: Post-stroke brain. Astrocytes are activated in and around the lesion, which inhibit neuroblast migration. Neuroblasts use Slit protein to clear the path of activated astrocytes through the transmembrane receptor Robo, but the number reaching the lesion is insufficient to induce functional recovery. Right: Slit overexpression in the post-stroke brain. Slit-overexpressing neuroblasts migrate efficiently toward the lesion through activated astrocytes, resulting in functional recovery. Credit: Kazunobu Sawamoto

More information: "New neurons use Slit-Robo signaling to migrate through the glial meshwork and approach a lesion for functional regeneration" advances.sciencemag.org/content/4/12/eaav0618

Provided by National Institutes of Natural Sciences