This Week in The Journal

Cyfp1 Suppresses Adult Neural Stem Cell Proliferation

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(see pages 2015–2024)

Neural stem cells (NSCs) residing in the subventricular zone in the wall of the lateral ventricle of adult rodents generate up to 10,000 neurons per day throughout the animal's life. To prevent premature depletion of the stem cell population, these NSCs (called B1 cells) must balance neuron generation with self-renewing proliferation and quiescence. Researchers long assumed that B1 cells achieved this balance through asymmetric cell divisions that produce one intermediate progenitor and one B1 cell; such asymmetric divisions underlie the ability of radial glial cells to produce the appropriate number of cortical neurons during embryonic development. Although B1 cells are derived from radial glia, recent work revealed that B1 cells typically undergo symmetric divisions, usually producing two intermediate progenitors, but sometimes producing two B1 cells. Newly generated B1 cells may remain quiescent for several months before dividing (Obernier et al., 2018, *Cell Stem Cell* 22:221). Many environmental cues are thought to influence whether a B1 cell remains quiescent or undergoes differentiating or self-renewing division; they do so by regulating protein expression at the transcriptional and translational levels. The details of these regulatory processes are poorly understood, but Habela et al. suggest that Cyfp1 is involved.

Cyfp1 is a cytoplasmic protein that interacts with the fragile X mental retardation protein to regulate protein translation. It also interacts with proteins that regulate actin polymerization, and it is essential for maintaining adherens junctions, which regulate proliferation of radial glial cells. Although Cyfp1 is widely downregulated in the ventricular zone after embryonic development, Habela et al. found that its expression persists in B1 cells. Knocking out Cyfp1 selectively in NSCs of adult mice led to an increase in B1 cell proliferation. This resulted in the abnormal presence of B1 somata at the ventricular surface. The additional cells expressed a marker of B1 cells but not a marker of neuroblasts or intermediate

precursors, suggesting that loss of Cyfp1 increased self-renewing division without altering differentiating division. Cyfp1 knockdown also disrupted the pattern of N-cadherin expression at cell–cell junctions at the ventricular surface.

These data suggest that Cyfp1 suppresses stem cell proliferation during adulthood. Whether this results from Cyfp1's effects on actin polymerization, protein translation, or both remains to be determined.

Eight days after Cyfp1 was knocked down in NSCs of adult mice (bottom), B1 cells (red) appeared on the ventricular surface and the expression pattern of N-cadherin (blue) was altered compared with that in controls (top). Arrowheads indicate the apical processes of B1 cells whose somata are beneath the ventricular surface. GFP expression (green) indicates Cre-mediated recombination. See Habela et al. for details.

Mitochondrial Gene Regulates Microglial Phagocytosis

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(see pages 2154–2165)

Intracerebral hemorrhage is a particularly deadly form of stroke. Blood rushing into the brain parenchyma after the hemorrhage compresses tissue, causing neuronal death. Subsequently, protein and cellular components of the blood, particularly red blood cells and hemoglobin, produce secondary injury, partly by promoting inflammation and causing oxidative stress. This damage is limited by microglia, which phagocytose red blood cells. Pro-

moting the phagocytic activity of microglia while limiting their proinflammatory activities may therefore improve outcomes after intracerebral hemorrhage. Mitochondria may hold the key to achieving this goal.

In the 2 billion years since mitochondria took up residence in eukaryotic cells, most mitochondrial genes have been incorporated into nuclear DNA. But mitochondria maintain a small genome that encodes proteins involved in ATP production, as well as several peptides. The first of these peptides to be discovered was humanin, which was identified in a screen for genes that protect neurons from toxic β -amyloid peptides. Humanin has subsequently been shown to protect neurons from a variety of other insults, including ischemic stroke (which results from blockage rather than rupture of blood vessels). Jung et al. now provide evidence that the rat homolog of humanin can limit damage in a model of intracerebral hemorrhage.

The authors found that humanin levels were significantly lower in the hemisphere subjected to intracerebral hemorrhage than in the contralateral hemisphere. But humanin injected intravenously improved motor function and sped hematoma clearance. Exogenous humanin was taken up by many brain cells, including microglia. The authors also found that cultured astrocytes released intact mitochondria into the culture medium, and that when this medium was transferred to microglial cultures, the mitochondria were rapidly taken up and increased humanin levels in microglia. Treating microglia with astrocytic mitochondria or humanin also reduced production of the proinflammatory molecule IL-1 β and increased expression of peroxisome proliferator receptor γ , a transcription factor that regulates important antioxidant genes and genes involved in phagocytosis. Consequently, microglial phagocytosis of red blood cells increased.

These results, along with previous work, present humanin as a promising candidate for treating numerous neurological conditions, including intracerebral hemorrhage. Future work should determine whether humanin reduces inflammation and promotes phagocytic activities *in vivo* as well as *in vitro*.

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