This Week in The Journal

● Cellular/Molecular

Neuronal Angiogenin Cleaves Astrocytic RNA

Alexandra Skorupa, Matthew A. King, Isabela M. Aparicio, Heiko Dussmann, Karen Coughlan, et al.

(see pages 5024 –5038)

Many molecules that regulate the vascular system also have roles in the nervous system. For example, semaphorins, originally identified as axon guidance molecules, also guide vascular patterning, and several angiogenic growth factors, including the secreted RNase angiogenin, promote neuronal survival. Skorupa et al. found that medium containing angiogenin enhanced survival of motor neurons subjected to AMPA-induced excitotoxicity in mouse ventral horn cultures. Surprisingly, although angiogenin was expressed solely by neurons in these cultures, its RNase function was restricted to astrocytes. Angiogenin uptake was mediated by the heparan-sulfate-proteoglycan-containing receptor syndecan 4, which is expressed selectively in glia. Subjecting cultures to stress by withdrawing serum stimulated secretion of angiogenin by neurons, increased angiogenin uptake by astrocytes, and induced RNA fragmentation in astrocytes. Blocking clathrin-mediated endocytosis prevented angiogenin uptake and RNA fragmentation. Interestingly, mutations in angiogenin that are associated with amyotrophic lateral sclerosis reduced angiogenin uptake and prevented RNase fragmentation.

▲ Development/Plasticity/Repair

LNK Limits Stem Cell Proliferation after Stroke

Henrik Ahlenius, Karthikeyan Devaraju, Emanuela Monni, Koichi Oki, Somsak Wattananit, et al.

(see pages 5151–5164)

Loss of blood supply to the brain causes neuronal death and loss of function. Spontaneous functional recovery often occurs, however, via synaptic plasticity, functional reorganization, angiogenesis, and neurogenesis. The latter two processes increase in parallel after stroke, and newborn neurons migrate beyond their normal destinations in the hippocampus and olfactory bulb to the site of injury. Although the extent to which neurogenesis contributes to functional recovery remains unclear, enhancing neurogenesis might prove beneficial. Ahlenius et al. have taken a step in this direction by showing that the adaptor protein LNK, which suppresses hematopoietic stem cell proliferation, also limits neural stem and progenitor cell (NSPC) proliferation after stroke. Their data support a model in which stroke activates the transcription factors STAT1 and STAT3, which induce LNK expression. LNK then inhibits the effects of growth factors that are upregulated after stroke—particularly insulin-like growth factor—at least in part by inhibiting activation of their downstream effector kinase, AKT.

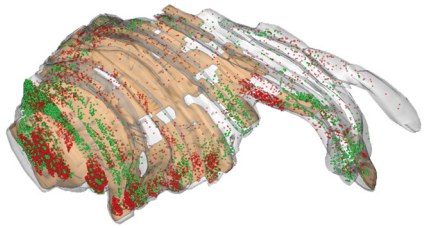
■ Behavioral/Systems/Cognitive

New Projection from Amygdala to Thalamus Is Found

Basilis Zikopoulos and Helen Barbas

(see pages 5338 –5350)

Prominent stimuli draw our attention, but executive control allows us to focus our attention on selected stimuli. The thalamic reticular nucleus (TRN), a thin sheet of cells surrounding the dorsal thalamus, has been proposed as a key hub in both processes. Most thalamic nuclei have reciprocal excitatory connections with specific cortical areas. These projections pass through and extend collaterals within the TRN, which principally contains GABAergic neurons that project to other thalamic nuclei. Strong input from one sensory modality or cortical area could hypothetically excite TRN neurons, causing them to inhibit transmission through other thalamic nuclei. How subtle but important stimuli—e.g., from an impending threat—capture attention has remained unclear, however. Zikopoulos and Barbas provide a possible answer by describing a hitherto undetected projection from the macaque amygdala—a key structure in processing emotional information—to the



Projections from the amygdala (green) and orbitofrontal cortex (red) converge on widespread areas of the TRN that project to the mediodorsal thalamic nucleus (brown shading). See the article by Zikopoulos and Barbas for details.

TRN. These projections overlapped with those from various cortical areas, potentially allowing interaction between inputs to focus attention appropriately.

♦ Neurobiology of Disease

Dementia-Linked Presenilin Mutation Causes Abnormal Splicing

Hirotaka Watanabe, Dan Xia, Takahisa Kanekiyo, Raymond J. Kelleher III, and Jie Shen

(see pages 5085–5096)

Presenilin is part of the γ-secretase complex that cleaves amyloid precursor protein (APP) to form β-amyloid (Aβ). Mutations in presenilin cause familial Alzheimer's disease (AD) and frontotemporal dementia (FTD), but how such mutations affect γ-secretase function is unclear. Accumulation of Aβ suggests that γ-secretase is overactive in AD, but some presenilin mutations produce FTD without amyloid plaques, suggesting γ-secretase function is diminished. Furthermore, γ-secretase has targets besides APP, notably the signaling molecule Notch, and preventing cleavage of these products—either by reducing γ-secretase activity or by increasing its APP load—might contribute to cognitive impairment in AD and FTD. To address this question, Watanabe et al. created knock-in mice harboring the presenilin mutation *c.548G>T*, which causes FTD without plaques. The mutation caused aberrant splicing of presenilin transcripts, resulting in loss of 1–2 exons and subsequent degradation. As a result, presenilin expression and cleavage of APP and Notch were reduced.