NEUROSCIENCE

Focus Issue: Uncovering the Mechanisms of Neurological Disease

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This week, *Science Signaling* highlights research that uses computational and cell biology approaches to uncover the molecular mechanisms underlying diseases of the central nervous system. In particular, research featured explores the neuronal response to stress due to excess excitatory stimuli, multiple roles for presenilin in Alzheimer's disease, and mechanisms through which autism may arise. In addition, new molecular targets for treating an aggressive form of brain cancer are presented. Not only do these articles provide potential mechanisms for the development of therapies, they also illuminate the intricacies of synaptic signaling and the complexity of forming and maintaining appropriate synaptic connections.

Neurons communicate through a synapse, formed by the close apposition of two cells. Synaptic transmission involves the release of neurotransmitters that modulate the activity of the postsynaptic neuron, resulting in either excitation or inhibition. Both the presynaptic neuron and the postsynaptic neuron contribute to synaptic plasticity, which is critical to learning and memory. Synaptic integrity is key to neuronal function and survival. The coordination of intracellular protein trafficking and calcium signaling contribute to synaptic integrity and plasticity.

Neurological diseases can arise from the failure to maintain or form appropriate synaptic connections; increased neuronal stress, which can occur from excessive excitatory stimulation or excitotoxicity; or, in the extreme situation, neuronal death. Some of the cellular changes associated with aberrant neuronal function include altered synaptic transmission and changes in postsynaptic receptor composition or abundance. Two culprits associated with excitotoxicity are calcium signaling and ionotropic glutamate receptors, which are calcium-permeable, ligand-gated ion channels. In a Review in the Archives, Prager and Johnson describe how glucocorticoids signaling through membrane-associated receptors affect neuronal excitabililty and synaptic transmission. Low doses of corticosterone acting at the membrane-associated mineralcorticoid receptor increase glutamatergic synaptic transmission, whereas higher doses acting at glucocorticoid membrane receptors decrease neuronal excitability. In a Research Article in this issue, Yang *et al*. report that the c-Jun N-terminal kinase 3 (JNK3) inhibits Golgi-mediated secretory trafficking in response to neuronal stress. In response to excitation with the glutamate receptor agonist NMDA, JNK3 was palmitoylated and localized to the Golgi where it sequestered Sac1, a phosphatase that metabolizes PI4P (phosphatidylinositol-4-phosphate). This action of JNK3 was independent of its kinase activity. The decreased abundance of PI4P in the Golgi inhibited the Golgi-to-surface trafficking of GluR1, an AMPA-type glutamate receptor, and reduced the number of synapses in cultures of rat hippocampal and cortical neurons. Whether this decrease in connectivity serves as a protective adaptation through which neurons minimize excitotoxicity or whether it is a undesirable consequence of excessive stimulation is not clear. Deregulation of this pathway may contribute to some neuronal diseases that are associated with synaptic loss. Disrupting the JNK3-Sac1 interaction with synthetic peptides decreased the stress-induced inhibition of secretory trafficking and synaptic loss.

Calcium is a critical component of neuronal signaling; however, at high concentrations calcium is toxic. Aberrant calcium signaling, thus, is a source of neuronal stress and can result in neuronal death. Alzheimer's disease (AD) is a form of cognitive dementia associated with neuronal loss, and, in the early stages of the disease, regions of the brain associated with short-term memory are particularly affected. A hallmark feature of AD is the deposition of a cleaved form of amyloid β (Aβ), which forms plaques in the brain. In a Perspective in the Archives, Liao and Xu discuss how intracellular Aβ inhibits insulin receptor signaling in neurons by interfering with the association between phosphoinositide-dependent kinase 1 (PDK1) and Akt1, preventing Akt1 activation. Insulin and insulin-sensitizing drugs improve cognitive and memory functions in animal models of AD, as well as in AD patients. Aβ production is increased by mutations in *PS1*, a gene that encodes presenilin-1, and these mutations in *PS1* cause early-onset familial AD. Two functions for presenilin have been proposed. At the plasma membrane, presenilin functions as part of a γ-secretase complex and produces Aβ. At the endoplasmic reticulum (ER), presenilin may contribute to calcium homeostasis, but this function has been controversial, as Bezprozvanny describes in a Perspective in this issue. Although calcium pumps in the ER and plasma membrane are primarily responsible for maintaining intracellular calcium at nontoxic concentrations, other proteins, channels, and exchangers are also important for maintaining calcium homeostasis. In a Research Article in the Archives, Cheung *et al*. (see also Mattson) describe how mutations in *PS1* exaggerated calcium flux at synaptic terminals by enhancing ER Ca^{2+} release, rendering neurons vulnerable to dysfunction and degeneration. Further, in a Research Article in this issue, Bandara *et al*. combine computational biology, single-cell live imaging, and an RNA-interference screen to provide a quantitative model of the major Ca^{2+} pumps and leak currents in cells. Their model identified presenilin-2 and the channel Orai2 as mediators of the ER Ca^{2+} leak, thus providing additional support for the hypothesis that dysregulation of this function of presenilins may contribute to AD.

Autism is a common neurodevelopmental disorder that affects information processing in the brain and is thought to be caused by altered synaptic connectivity. Autism may be nonsyndromic or syndromic depending on whether it is associated with genetic mutations, such as fragile X syndrome, which alters dendritic structure. Deficiency or mutation of the postsynaptic adhesion proteins neuroligins may contribute to autism by changing the balance of excitatory and inhibitory synapses. In a Review in this issue, Singh and Eroglu integrate the findings from several neuroligin studies into a model of how neuroligins mediate synaptic connectivity in the CNS and propose that neuroligins may connect the pathophysiologies of syndromic and nonsyndromic autism. Indeed as Singh and Eroglu mention, studies with mice showed that the neurological changes associated with

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loss of neuroligin function may be amenable to treatment after development, which provides hope that therapies for both young and older autism patients is possible.

Glial cells are also critical to proper CNS function. Loss of oligodendrocyte function results in demyelination, which causes diseases such as multiple sclerosis. Understanding how to effectively target inflammatory pathways contributing to multiple sclerosis was the topic of the Perspective by Steinman and Research Article by Inoue *et al*. in the Archives. Deregulated proliferation of glia results in some of the most aggressive forms of cancer, such as glioblastoma multiforme (GBM). Understanding the molecular mechanisms responsible for glioma and how to effectively target the dysregulated signaling pathways has been the topic of several Research Articles and a Review in the Archives. As reviewed by Huang *et al*., GBM harbors mutations in EGFR (epidermal growth factor receptor) that confers rapid cancer cell proliferation, diffuse invasion, and chemoresistance. GBM that have concurrent mutations in PTEN (phosphatase and tensin homolog) are difficult to treat with current EGFR-targeted therapies. Fan *et al*. (2010) and Fan *et al*. (2009) implicated the mTOR (mechanistic target of rapamycin) pathway and autophagy as viable targets for treating glioma. Tibarewal *et al*. showed that both the protein and lipid phosphatase activity of PTEN were important for the invasive properties of glioma. In a Research Article in this issue, He *et al*. show that an allosteric inhibitor of the Janus kinase 2 (JAK2) is more effective at inhibiting the proliferation of this aggressive glioma than are catalytic inhibitors of JAK2 or mutant EGFR. The synthetic chemical, named G5-7, selectively blocked JAK2-mediated activation of EGFR and STAT3 (signal transducer and activator of transcription 3). Structure-activity analysis showed that modifying certain aspects of G5-7 may further improve the inhibition of glioma proliferation without affecting that of normal neurons and astrocytes, suggesting the possibility for future clinical development.

The research highlighted here indicates that understanding the complex molecular mechanisms underlying normal and pathological neuronal function will enable improved clinical targets or agents for patients in the future.

Featured in This Issue

Research Articles

- K. He, Q. Qi, C.-B. Chan, G. Xiao, X. Liu, C. Tucker-Burden, L. Wang, H. Mao, X. Lu, F. E. McDonald, H. Luo, Q.-W. Fan, W. A. Weiss, S.-Y. Sun, D. J. Brat, K. Ye, Blockade of glioma proliferation through allosteric inhibition of JAK2. *Sci. Signal.* **6**, ra55 (2013).
- S. Bandara, S. Malmersjö, T. Meyer, Regulators of calcium homeostasis identified by inference of kinetic model parameters from live single cells perturbed by siRNA. *Sci. Signal.* **6**, ra56 (2013).
- G. Yang, X. Zhou, J. Zhu, R. Liu, S. Zhang, A. Coquinco, Y. Chen, Y. Wen, L. Kojic, W. Jia, M. S. Cynader, JNK3 couples the neuronal stress response to inhibition of secretory trafficking. *Sci. Signal.* **6**, ra57 (2013).

Review

- S. K. Singh, C. Eroglu, Neuroligins provide molecular links between syndromic and nonsyndromic autism. *Sci. Signal.* **6**, re4 (2013).

Perspective

- I. Bezprozvanny, Presenilins and calcium signaling—Systems biology to the rescue. *Sci. Signal.* **6**, pe24 (2013).

Podcast

- K. Ye, A. M. VanHook, *Science Signaling* Podcast: 9 July 2013. *Sci. Signal.* **6**, pe17 (2013).

Related Resources

Research Articles

- K.-H. Cheung, L. Mei, D.-O. D. Mak, I. Hayashi, T. Iwatsubo, D. E. Kang, J. K. Foskett, Gain-of-function enhancement of IP_3 receptor modal gating by familial Alzheimer's disease–linked presenilin mutants in human cells and mouse neurons. *Sci. Signal.* **3**, ra22 (2010).
- Q.-W. Fan, C. Cheng, Z. A. Knight, D. Haas-Kogan, D. Stokoe, C. D. James, F. McCormick, K. M. Shokat, W. A. Weiss, EGFR signals to mTOR through PKC and independently of Akt in glioma. *Sci. Signal.* **2**, ra4 (2009).
- Q.-W. Fan, C. Cheng, C. Hackett, M. Feldman, B. T. Houseman, T. Nicolaides, D. Haas-Kogan, C. D. James, S. A. Oakes, J. Debnath, K. M. Shokat, W. A. Weiss, Akt and autophagy cooperate to promote survival of drug-resistant glioma. *Sci. Signal.* **3**, ra81 (2010).
- M. Inoue, K. L. Williams, T. Oliver, P. Vandenabeele, J. V. Rajan, E. A. Miao, M. L. Shinohara, Interferon-β therapy against EAE is effective only when development of the disease depends on the NLRP3 inflammasome. *Sci. Signal.* **5**, ra38 (2012).
- P. Tibarewal, G. Zilidis, L. Spinelli, N. Schurch, H. Maccario, A. Gray, N. M. Perera, L. Davidson, G. J. Barton, N. R. Leslie, PTEN protein phosphatase activity correlates with control of gene expression and invasion, a tumor-suppressing phenotype, but not with AKT activity. *Sci. Signal.* **5**, ra18 (2012).

Reviews

- E. M. Prager, L. R. Johnson, Stress at the synapse: Signal transduction mechanisms of adrenal steroids at neuronal membranes. *Sci. Signal.* **2**, re5 (2009).
- P. H. Huang, A. M. Xu, F. M. White, Oncogenic EGFR signaling networks in glioma. *Sci. Signal.* **2**, re6 (2009).

Perspectives

- M. P. Mattson, ER calcium and Alzheimer's disease: In a state of flux. *Sci. Signal.* **3**, pe10 (2010).
- F. F. Liao, H. Xu, Insulin signaling in sporadic Alzheimer's disease. *Sci. Signal.* **2**, pe36 (2009).
- L. Steinman, Inflammatory cytokines at the summits of pathological signal cascades in brain diseases. *Sci. Signal.* **6**, pe3 (2013).

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