NEUROSCIENCE

Focus Issue: New horizons for treating neurological disease

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This issue of *Science Signaling* highlights research that uncovers protein interaction networks and potential drug targets, as well as research that identifies molecular mechanisms of action of novel or existing drugs, for neurological and psychological disease. This Editorial Guide features a handful of papers from 2016 that join the ranks of *Science Signaling*'s vast archive of articles related to neuroscience.

A barrier to treating patients with neurological and psychological disease has been the difficulty of getting to the molecular underpinnings of the disease within the physiological context, the brain in the living patient. Recent and emerging advances in technology—from proteomics to optogenetics and other in vivo techniques—open the door to a deeper understanding of neurophysiology, the identification of the molecular origins of disease, and the development of better, more targeted therapeutics for patients. *Science Signaling* has a vast archive of articles related to neuroscience. Here, we highlight select articles from 2016 that reveal how kinases and protein interaction networks are keys to treating many neurological diseases. In this week's issue, Licht-Murava *et al.* identified a peptide that might be used to treat patients with Alzheimer's disease (AD). Glycogen synthase kinase 3 (GSK-3) is a serine/threonine kinase that recognizes phosphorylated prolines in its substrates and is implicated in various neurodegenerative diseases, including AD. However, competitive GSK-3 inhibitors have failed to reach the clinic because of a lack of specificity. Peptides that disrupt kinase-substrate interactions are an alternative to catalytic inhibitors. Licht-Murava *et al.* developed a derivative of a GSK-3 substrate peptide that becomes a catalytic inhibitor when phosphorylated by GSK-3. This peptide, called L807mts, improved neuropathological symptoms and cognitive behavior in an AD mouse model. The substrate-to-inhibitor conversion mechanism might afford the selectivity needed to make L807mts or its derivatives viable GSK-3 inhibitors for patients. From the signaling and drug development perspectives, this represents a novel mechanism of kinase inhibition that could lead to the development of other selective kinase inhibitors with this type of mechanism.

Indeed, kinases are implicated in many other neurological disorders. For example, Kashima *et al.* identified a potential strategy that involves targeting the kinase LIMK1 to treat the cognitive disorder fragile X syndrome (FXS). FXS is caused by loss of the RNA binding protein FMRP. Loss of FMRP increased the stability and translation of the FMRP target transcript encoding a bone morphogenetic protein receptor, BMPR2. BMPR2, in turn, triggered the activation of the kinase LIMK1, which inhibited cytoskeletal processing necessary for the maturation of dendritic spines. LIMK1 inhibitors restored spine maturation in genetically modified mouse and *Drosophila* models. Because spine development is crucial for learning and memory, selectively targeting LIMK1 might ameliorate the cognitive impairments seen in FXS patients.

Kinase signaling pathways have also been implicated in pain conditions. Chronic pain is a debilitating condition that contributes to psychological disorders such as depression. Currently available painkillers can be highly addictive. In the Archives, articles by Kahle *et al.* studied neuropathy-associated mutations to reveal potential strategies to treat chronic pain involving proteins regulated by the pathway activated by the kinase WNK (with-no-lysine). In one article, Kahle and colleagues discovered a point mutation in the gene encoding the K^+-Cl^- transporter KCC3 in a patient with an early-onset, progressive, and severely disabling peripheral neuropathy. The mutation in KCC3 prevents inhibition by WNK-dependent signaling in peripheral neurons. In another article, Kahle and other colleagues show that a spinal cord–localized, alternatively spliced variant of WNK1 promotes neuropathic pain. Deletion of the HSN2 exon in this WNK1 variant or inhibition of WNK1 prevented cold and mechanical hypersensitivity in mice with peripheral nerve injury, suggesting that specific inhibition of either this form of WNK1 or WNK1 signaling in peripheral nerves should be explored as a treatment for some patients with neuropathic pain. Furthermore, these papers showed that WNK regulates synaptic activity and neuronal health through effects on Cl^- balance in peripheral neurons. The WNK-dependent pathway has roles in other physiological contexts (such as hypertension), and developing inhibitors of this pathway represents a promising therapeutic strategy (see the Perspective by Zhang *et al.*). However, general WNK pathway inhibitors may have undesirable nervous system side effects, such as enhancement of pain perception or aggravation of neuropathy; thus, carefully designed dosing regimens, target specificity, and patient stratification are important considerations for applying WNK pathway–targeted drugs.

Additionally, protein interaction networks and their dynamics in neurons are emerging as rich resources for understanding the complexities of behavior and disease and the mechanisms of drug action. These studies also yield candidate targets for future drug development. In this issue of *Science Signaling*, Shahani *et al.* used mice to identify protein interaction networks centered on the guanosine triphosphatase Rhes. These networks are involved in the control of locomotor activity by the striatum. Both the stimulant amphetamine and the guanine exchange factor RasGRP1 altered the proteins with which Rhes interacted, including several that are associated with various neurological diseases. Rhes is itself implicated in Huntington's disease. Amphetamine and drugs like it could be beneficial in various neurological and psychological disorders characterized by impaired dopamine signaling in the striatum, such as Huntington's disease, Parkinson's disease, narcolepsy, and attention deficit hyperactivity disorder. Thus, the findings reveal the molecular underpinnings of amphetamine's locomotor effects as well as mechanisms through which Rhes may contribute to motor disorders such as Huntington's disease. Furthermore, this study illustrates the dynamic nature of protein interaction networks and how drugs can cause their reorganization.

The postsynaptic region of neuron is a highly organized structure containing so many proteins (more than 1500 different ones) that

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it appears dense in electron micrographs and thus is called the postsynaptic density (PSD). Yet, synapses are highly dynamic and long-term changes in synaptic strength are considered molecular correlates of learning and memory. Li *et al*. isolated and analyzed protein interaction networks within the PSD from the mouse hippocampus upon induction of long-term potentiation (LTP, a form of synaptic plasticity). They found that risk factors associated with autism spectrum disorder and schizophrenia were contained within LTP-regulated phosphoproteins. These data should guide researchers and clinicians toward a better understanding of both the molecular changes that enable learning and memory and the complex neurological diseases involving proteins that are part of the PSD.

Protein interaction networks typically involve proteins that function as molecular scaffolds. Some proteins have multiple functional domains, such as catalytic domains, protein interaction domains, and scaffolding domains. PSD-95 is a critical scaffolding protein that contains protein-interacting PDZ domains and helps organize the PSD. Alfonso *et al.* (with an associated Podcast) found that activity of the protein kinase Cα (PKCα) mediates β amyloid–induced synaptic impairment, as seen in patients with AD. This role of PKCα involved its PDZ-binding domain, suggesting that PDZ proteins, such as PSD-95, recruit this kinase to the synapse. These data provide a mechanism for how gain-of-function variants in *PRKCA*, the gene encoding PKCα, which were identified in five families with late-onset AD, may contribute to the disease. With the advances in the ability to identify specific protein interactions and localize these interactions to specific regions within cells, we anticipate that studies of protein interaction networks in both peripheral and central neurons will yield clues to better therapies for various neurological diseases.

RELATED RESOURCES

Research Articles

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Research Resources

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Perspective

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Podcast

- A. C. Newton, R. E. Tanzi, A. M. VanHook, *Science Signaling* Podcast for 10 May 2016: PKCα in Alzheimer's disease. *Sci. Signal.* **9**, pc11 (2016).

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