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Uncovering a Role for SK2 in Angelman Syndrome

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Angelman syndrome is a severe neurodevelopmental disorder caused by mutations in UBE3A. Sun et al. (2015) report SK2 as a UBE3A substrate and provide insight into the molecular mechanisms that might underlie impaired neuronal function in individuals affected by Angelman syndrome.

Angelman syndrome (AS) affects somewhere from 1 in 10,000 to 1 in 20,000 people (Bird, 2014). This neurodevelopmental disorder is characterized by an unusually happy demeanor, severe intellectual disability, speech impairment, ataxia, and refractive epilepsy and may be associated with autistic symptoms (Bird, 2014). AS is caused by deletions or point mutations involving the maternally inherited copy of *UBE3A*, which encodes a HECT domain-containing ubiquitin E3 ligase (Jiang et al., 1999; Margolis et al., 2015; Mabb and Ehlers, 2010). The covalent addition of ubiquitin to a lysine residue in targeted proteins regulates their localization, stability, endocytosis, and function (Mabb and Ehlers, 2010). Mouse models for AS exhibit impaired learning and memory, defects in dendritic spine morphology, reduced hippocampal long-term potentiation (LTP), and deficiencies in experience-dependent cortical plasticity (Yashiro et al., 2009). Despite the importance of UBE3A in neuronal development and function, only a limited number of UBE3A neuronal substrates have been identified (Greer et al., 2010; Margolis et al., 2010). In this issue of *Cell Reports*, Sun et al. shine a bright light on the molecular mechanisms underlying UBE3A-dependent synaptic plasticity, learning, and memory. Using a multi-pronged approach, they demonstrate that SK2 (small-conductance Ca^{+2}-activated K^+ channel 2) is a substrate of UBE3A, suggesting that UBE3A might regulate cognitive function through SK2. Their findings also identify a potential therapeutic approach for the treatment of AS.

Calcium (Ca^{+2}) signaling is essential for synaptic activity. SK channels are potassium channels that are activated by increased submicromolar concentrations of intracellular Ca^{+2}. These channels (SK1, SK2, and SK3) are widely expressed in the CNS, where they modulate synaptic transmission and the induction of synaptic plasticity to impact learning and memory (Adelman et al., 2012). SK channels are therefore extremely important for normal cognitive function. SK2 is a postsynaptic multiprotein complex that contains four pore-forming subunits and constitutively bound calmodulin (CaM), protein kinase CK2, and protein phosphatase A2 (PP2A) (Adelman et al., 2012). In hippocampal pyramidal neurons, SK2 regulates neuronal excitability and the threshold for LTP induction (Adelman et al., 2012). However, very little is currently known about how SK2 localization and function are regulated at the synapse.

Using a variety of in vitro and in vivo approaches, Sun et al. show that UBE3A-deficient (AS) mice have increased levels of SK2 at the synapse (Sun et al., 2015). The specific increase of SK2 in dendritic structures does not correspond to a global increase in SK2 expression; instead, the direct interaction between SK2 and UBE3A suggests that SK2 levels may be regulated by ubiquitin-mediated degradation or endocytocis. In fact, SK2 ubiquitination is significantly decreased in AS animals in comparison to controls. Ubiquitination of the SK2 C-terminal domain is mediated by UBE3A activity at lysine residues K506, K515, and K550 downstream of the CaM binding site. More importantly, UBE3A-mediated ubiquitination at these residues regulates the surface expression and endocytosis of SK2 in hippocampal neurons.

AS mice have impaired LTP, which has been linked to increased internalization of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs); this increased internalization is caused in part by increased levels of the synaptic protein ARC, a substrate of UBE3A in vitro (Greer et al., 2010). UBE3A-mediated degradation of Ephexin5 promotes the development of excitatory synapses, suggesting an additional mechanism through which synaptic plasticity and transmission might be affected in AS-affected individuals (Margolis et al., 2010). SK2 channels have previously been shown to modulate the induction of synaptic plasticity, and blocking SK2 channels with its specific inhibitor, Apamin, was shown to facilitate induction of LTP in CA1 hippocampal neurons (Adelman et al., 2012). Sun et al. now show that theta-burst stimulation (TBS)-induced LTP is dependent on SK2 activity in AS mice. Acute exposure of hippocampal slices to Apamin restores TBS-LTP levels in AS hippocampal slices to levels similar to those in wild-type slices. The importance of UBE3A-mediated SK2 ubiquitination to hippocampal LTP

is further shown in vivo by treatment of wild-type animals with a SK2 peptide containing K550, given that wild-type animals treated with this peptide mimic the LTP impairment in AS mice. Similar approaches to the ones described above reveal that long-term depression (LTD), an activity-dependent reduction in synaptic strength important for learning and memory, is also impacted by SK2 function in AS mice. LTP and LTD cellular processes require the activation of AMPARs and N-methyl-D-aspartate receptors (NMDARs) at the synapse, and SK2 is activated by Ca^{+2} release after NMDAR activation, resulting in the reduction and/or blockage of NMDAR-dependent Ca^{+2} signaling (Adelman et al., 2012). Here, pharmacological isolation of NMDAR function—either by blocking AMPARs with CNQX or by use of the AP5-a NMDAR antagonist—shows that SK2-dependent LTP and LTD defects in AS mice require NMDAR function.

The relevance of SK2 function to learning and memory is highlighted by the fact that Apamin treatment of wild-type animals enhances their performance in the water-maze learning test (Adelman et al., 2012). Building on these molecular and physiological findings, the authors probe further into the role of SK2 in AS-associated cognitive impairments by conducting behavioral analysis. Context-dependent fear-conditioning paradigms are severely compromised in AS mice, and treatment of AS mice with Apamin leads to a significant improvement in context- and cue-dependent learning. These findings represent a significant advancement in our understanding of the underlying mechanisms that control cognitive impairment in individuals with AS and identifies a potential therapeutic target for treatment.

Like a symphony conductor, UBE3A-mediated endocytosis of postsynaptic proteins carefully orchestrates the function of multiple synaptic pathways that are important for learning and memory. On the basis of the similarities between Apamin and BDNF effects on learning and memory (Adelman et al., 2012), as well as reported defects in BDNF-TrkB signaling in AS (Cao et al., 2013), one might someday ask, "What is the potential link between SK2 and BDNF signaling in AS pathophysiology?" By identifying SK2 as a target of UBE3A, this study unveils a new aspect of the molecular pathology in AS, which will lead to new lines of investigation with relevance to disease treatment and cognition.

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