My Unexpected Journey to Basic Research of Autism: The Relevance to Precision Nutrition

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My laboratory has a long-term interest in exploring how genes control neuronal morphology and activity and thereby regulate neural circuit formation and behaviors. We have been focusing on causative genes for neurodevelopmental disorders (ND), especially autism spectrum disorders (ASD), because ASD arises from aberrant neural development, which consequently results in abnormal neural connectivity and behaviors. We have been using genetically modified mouse models and cultured hippocampal and cortical neurons and applying them to investigate how mutations of causative genes for ASD alter molecular functions of ASD-linked genes, influence neuronal morphology and function and result in abnormal mouse behaviors. In this lecture, I will summarize our study on cortactin-binding protein 2 (CTTNBP2). As a neuron-specific cytoskeleton binding protein, CTTNBP2 controls the formation and maintenance of excitatory synapses in cultured neurons and brains. Echoing human genetic study of ASD, *Cttnbp2* mutations result in autism-like behaviors in mice. Importantly, we showed that CTTNBP2 binds zinc and controls zinc homeostasis in the brains. In Cttnbp2 deficient mice, zinc supplementation improves social behavior. Moreover, we found that CTTNBP2 forms biological condensates at synapse via liquid-liquid phase separation (LLPS) and that zinc binding induces the liquid-to-gel phase transition of CTTNBP2. The LLPS and phase transition are critical regulatory processes to control the synaptic distribution of CTTNBP2. Interestingly, ASD-linked mutations of CTTNBP2 impair phase separation and synaptic distribution of CTTNBP2. The addition of zinc rescues the synaptic distribution of mutated CTTNBP2 proteins, echoing the rescue effect of zinc on mouse behaviors. Our study suggests the relevance of condensate formation and zinc-induced phase transition to the synaptic distribution and function of ASD-linked proteins and provides an example of precision nutrition for potential ASD therapeutics.