Genetic and environmental risks for autism

Mark Zylka, PhD
Department of Cell Biology and Physiology
University of North Carolina – Chapel Hill

Genetic and environmental factors are implicated in autism risk. One of the most commonly affected genes associated with autism is UBE3A. Notably, deletion of UBE3A causes the neurodevelopmental disorder Angelman syndrome (AS) while duplication or triplication of UBE3A is linked to autism. These genetic findings suggest that the ubiquitin ligase activity of UBE3A must be tightly maintained to promote normal brain development. We found that protein kinase A (PKA) phosphorylates UBE3A in a region outside the catalytic domain, at residue T485, and inhibits UBE3A activity towards itself and other substrates. A de novo autism-linked missense mutation disrupts this phosphorylation site, causing enhanced UBE3A activity in vitro, enhanced substrate turnover in patient-derived cells, and excessive dendritic spine development in the brain. Our research identifies PKA as an upstream regulator of UBE3A activity, and shows that an autism-linked mutation disrupts this phosphorylation control. Moreover, our findings implicate excessive UBE3A activity and the resulting synaptic dysfunction to autism pathogenesis. Environmental factors, including pesticides, have been linked to autism and neurodegeneration risk using retrospective epidemiological studies. We sought to prospectively identify chemicals that share transcriptomic signatures with neurological disorders by exposing mouse cortical neuron-enriched cultures to hundreds of chemicals commonly found in the environment and on food. We found that rotenone, a pesticide associated with Parkinson's disease risk, and certain fungicides, including pyraclostrobin, trifloxystrobin, famoxadone, and fenamidone, produce transcriptional changes in vitro that are similar to those seen in brain samples from humans with autism, advanced age and neurodegeneration (Alzheimer's disease, Huntington's disease). These chemicals stimulate free radical production and disrupt microtubules in neurons, effects that can be reduced by pretreating with a microtubule stabilizer, an antioxidant, or with sulforaphane. Our research provides a way to prospectively identify environmental chemicals that transcriptionally mimic autism and other brain disorders.