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SnapShot: Autism and the Synapse

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Autism and autism spectrum disorders (ASDs) are neurodevelopmental disorders diagnosed based on a triad of criteria: deficits in language and communication; impaired or abnormal social interactions; and restricted interests or repetitive behaviors. The high heritability of ASDs—up to 90% in monozygotic twins—when taken in conjunction with the prominence of ASDs in genetic syndromes (e.g., tuberous sclerosis complex [TSC], fragile X, Angelman, Phelan-McDermid) indicates that genetic factors play a key role in the etiology of these disorders. Additionally, recent work has identified several synaptic genes as candidates that may afford susceptibility to ASDs.

Findings from human genetic studies and functional neurobiological inquiries are coalescing in a map of the molecular pathways that when disrupted may be responsible for the origination of ASDs. In addition, the accretion of these findings has provided important insights concerning how a relatively broad group of neurodevelopmental disorders, with putative diverse genetic etiologies, may converge upon common proteins found at the synapse.

The Neurexin/Neuroligin/PSD95/SAPAP/Shank Pathway

Neurexins are cell-adhesion molecules located at the presynaptic membrane that bind to postsynaptic neuroligins across the synaptic cleft. Within the postsynaptic compartment, neuroligins in turn bind to the PSD95 family of proteins that then interact with SAPAP and Shank proteins. Notably, mutations in several genes encoding these families of postsynaptic proteins are implicated in ASD susceptibility. Among these, Shank3 is strongly associated with not only ASDs but also the Phelan-McDermid syndrome, which is known to be caused by 22q13 chromosomal microdeletions encompassing the Shank3 locus. At the synapse, Shank proteins are postulated to form a polymeric mesh of interactions. By assembling with Homer tetramers, Shank is well positioned to bridge ionotropic and metabotropic glutamate receptors and thus forms a central component in the postsynaptic density.

Fragile X Syndrome

Mutations in the fragile X mental retardation 1 (Fmr1) gene give rise to the most common form of heritable intellectual disability in humans. Additionally, a substantial percentage of fragile X syndrome patients display autistic behaviors making Fmr1 mutations the single most common known cause for autism. The most prevalent genetic lesion in the Fmr1 gene is expansion of CGG repeats that induce silencing in the production of fragile X mental retardation protein (FMRP). In neurons, FMRP associates with mRNA transcripts and promotes translational repression. Evidence suggests a direct link between FMRP and other ASD-relevant molecules, such as SAPAP, Shank, and TSC mRNAs.

Ubiquitin Genes

The 15q11-13 chromosomal regions are associated with ASD and, depending on paternal or maternal inheritance of certain genetic lesions, with Angelman Syndrome or Prader-Willi Syndrome. From the multiple genes affected in 15q11-13,UBE3A has been validated as causative to Angelman Syndrome and in copy number variation (CNV) findings for ASD susceptibility. Other genes involved in the ubiquitin pathway (PARK2, RFWD2, and FBX040) have also been implicated in a genome-wide CNV study for ASD. Shank and SAPAP proteins are among the few known targets in the postsynaptic density that are greatly influenced by the ubiquitin system in response to changing levels of synaptic activity. At the same time, it was recently found that mutations in the Shank3 gene causing the expression of a truncated protein induce ubiquitination and abnormal protein turnover of other Shank3 isoforms and of NMDA receptors at the synapse. It is clear that the tight regulation of synaptic protein levels is crucial for normal neuronal function with local proteins synthesis playing an opposing role to ubiquitination and proteasomal degradation.

Tuberous Sclerosis Complex

TSC is a genetic disease that is characterized by the appearance of nonmalignant tumors in the brain and other organs. A significant percentage of patients display autistic behaviors, mental retardation, and seizures. Two gene loci are associated with TSC, TSC1 and TSC2, which give rise to the proteins hamartin and tuberin, respectively. Hamartin and tuberin work in a complex to inhibit the function of the mammalian target for rapamycin (mTOR) that in turn regulates signaling pathways involved in cell growth and transcriptional activation. A recent study reports several binding partners in common between the TSC protein complex and Shank3 interactome. Among others, Shank1, Actin9, and Homer3 were shown to potentially mediate interactions between Shank3 and TSC1.

REFERENCES


