



Autism spectrum disorder causes, mechanisms, and treatments: focus on neuronal synapses

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Autism spectrum disorder (ASD) is a group of developmental disabilities characterized by impairments in social interaction and communication and restricted and repetitive interests/behaviors. Advances in human genomics have identified a large number of genetic variations associated with ASD. These associations are being rapidly verified by a growing number of studies using a variety of approaches, including mouse genetics. These studies have also identified key mechanisms underlying the pathogenesis of ASD, many of which involve synaptic dysfunctions, and have investigated novel, mechanism-based therapeutic strategies. This review will try to integrate these three key aspects of ASD research: human genetics, animal models, and potential treatments. Continued efforts in this direction should ultimately reveal core mechanisms that account for a larger fraction of ASD cases and identify neural mechanisms associated with specific ASD symptoms, providing important clues to efficient ASD treatment.

Keywords: autism spectrum disorder, therapeutics, genetics, animal model, synapse, synaptopathy

INTRODUCTION TO AUTISM SPECTRUM DISORDER

Autism spectrum disorder (ASD) is a group of developmental disabilities characterized by abnormal social interaction and communication, and stereotyped behaviors with restricted interest. Autism was first reported by Kanner (1943) with a clinical description of 11 children showing “extreme aloneness from the very beginning of life, not responding to anything that comes to them from the outside world.” He proposed the behavioral combination of autism, obsessiveness, stereotypy, and echolalia as childhood schizophrenia. However, until the 1980s, ASD was not accepted as an individual developmental disorder with a biological origin. In the early 1980s, studies demonstrated the high heritability of ASD and its association with other genetic syndromes (Gillberg and Wahlstrom, 1985; Wahlstrom et al., 1986), providing compelling evidence for a genetic etiology of ASD and fueling the conceptualization of autism as a distinct neurodevelopmental disorder. From the definition of “childhood or early-onset schizophrenia” put forward by Kanner, autism was renamed “infantile autism” in 1980, “autism disorder” in 1987 and, more recently, “autism” or the umbrella term “ASD”.

DIAGNOSIS

Currently, ASD is included in the diagnostic category of a neurodevelopmental disorders in the Diagnostic and Statistical Manual of Mental Disorders V (Grzadzinski et al., 2013). The diagnosis of autism is mainly based on the presence of two major aforementioned symptoms: social-communication deficits, and restricted and repetitive interests/behaviors (Grzadzinski et al., 2013). These symptoms must be shown from early childhood of individuals with ASD. But autism is also associated with various comorbidities, including sensory and motor abnormalities, sleep disturbance, epilepsy, attention deficit/hyperactivity

disorder (ADHD)-like hyperactivity, intellectual disability, and mood disorders such as anxiety and aggression (Goldstein and Schwabach, 2004; Simonoff et al., 2008; Geschwind, 2009). Some monogenic syndromes including fragile X syndrome and Rett syndrome also have autistic features, while we should be cautious to directly interpret the disorders as autism since the major symptoms for these syndromes are intellectual disabilities.

PREVALENCE

An early study conducted in the UK in 1966 reported a prevalence rate of autism of 4.5 in 10,000 children (Lotter, 1966). The estimated prevalence increased to 19 in 10,000 American children in 1992 and rose steeply to 1 in 150 in 2002 (Autism et al., 2007) and 1 in 110 in 2006 (Autism et al., 2009) (see also data from the US Centers for Disease Control and Prevention [CDC]). The currently accepted prevalence of ASD, based on consistent reports of ASD prevalence by multiple sources in different populations, is ~1% worldwide, placing this disorder as one of the most common pervasive developmental disorders and elevating public concerns.

GENETICS

On the basis of numerous studies that have been undertaken to elucidate the pathogenic mechanisms underlying ASD, it is widely accepted that ASD is a disorder with strong genetic components. In support of this notion, the concordance rates for autism reach up to 90% in monozygotic twins and 10% in dizygotic twins (Rutter, 2000; Folstein and Rosen-Sheidley, 2001; Veenstra-Vanderweele et al., 2003).

However, autism is an etiologically heterogeneous disorder in that no single genetic mutation accounts for more than 1–2% of ASD cases (Abrahams and Geschwind, 2008). Thus

far, linkage and candidate-gene analyses, genome-wide association studies (GWAS), and assessments of chromosomal variations have uncovered a wide range of genes with predisposing mutations and polymorphisms associated with ASD (International Molecular Genetic Study of Autism, 1998, 2001; Abrahams and Geschwind, 2008; Glessner et al., 2009; Ma et al., 2009; Wang et al., 2009; Weiss et al., 2009; Anney et al., 2010; Pinto et al., 2010; Devlin and Scherer, 2012; Moreno-De-Luca et al., 2013) (see **Tables 1, 2** for examples). Moreover, recent advancements in exome sequencing and next-generation sequencing have enabled the discovery of an overwhelming number of *de novo* mutations that confer a risk for ASD (Iossifov et al., 2012; Neale et al., 2012; O’Roak et al., 2012a,b; Sanders et al., 2012). These mutations include rare mutations or copy number variations in synaptic proteins such as Shanks/ProSAPs (Durand et al., 2007; Berkel et al., 2010; Sato et al., 2012) and neuroligins (Jamain et al., 2003).

However, how these mutations lead to ASD phenotypes is poorly understood. In addition, many ASD-related genes are also associated with other neuropsychiatric disorders. For example, *IL1RAPL1* and *OPHN1* are associated with X chromosome-linked intellectual disability (Billuart et al., 1998a; Carrie et al., 1999). Additional examples include schizophrenia for *RELN*, *GluR6*, *GRIN2A*, *GRIN2B*, and *CNTNAP2* (Bah et al., 2004; Friedman et al., 2008; Shifman et al., 2008; Demontis et al., 2011), childhood absence epilepsy for *GABRB3* (Feucht et al., 1999), ADHD and depression for *5-HTT* (Manor et al., 2001; Caspi et al., 2003), and major depression for *TPH2* (Zill et al., 2004). Dissecting the neural mechanisms underlying diverse symptoms/disorders caused by single genetic defects is one of the key directions for neuropsychiatric research.

ANIMAL MODELS FOR ASD

Animal models of human diseases need to satisfy three major criteria; face validity, construct validity, and predictive validity. Animal models for ASD should display behavioral abnormalities, including impaired sociability, impaired social communication, and repetitive and restricted behaviors (face validity). These models should share analogous genetic or anatomical impairments with humans (construct validity), and show similar responses to the medications used to treat ASD in humans (predictive validity).

Dedicated efforts of many behavioral neuroscientists including Jacqueline Crawley led to the establishment of several well-known assays for rat/mouse models of ASD (Silverman et al., 2010b). Examples include 3-chambered test to assess sociability and social novelty recognition of rodents, ultrasonic vocalization (USV) test to measure the communication patterns of rodents, *T*-maze test for restricted interests, and home cage behavior or marble burying assay for repetitive behaviors. Through these assays, many genetic and non-genetic animal models of ASD have been characterized and used to identify the etiology of ASD and develop novel treatments (see **Tables 3–6** for four different groups of ASD models).

Although animal models are useful for exploring ASD mechanisms and testing novel interventions, we should be cautious in interpreting the results from animal models of ASD because what we are observing in animals are behavioral features that look similar to some of the ASD symptoms in humans. This notion partly stems from the fact that the brains of humans and rodents are fundamentally different. For instance, there are small but significant differences in gene expression patterns in the cerebral cortex in different species (Zeng et al., 2012), suggesting that the

Table 1 | Examples of ASD-associated chromosomal loci and candidate genes from GWAS.

Chromosomal loci	Candidate genes	Sample size	Design	Population	References
4p, 7q, 16p	<i>GPR37</i> , <i>PTPRZ1</i> , <i>EPHB6</i> , <i>PTN</i> , <i>CASP2</i> , <i>GRM8</i> , <i>EAG</i> in 7q region	87 affected sib pairs and 12 non-sib affected relative pairs	Family	99 Caucasian families (66 from the UK, 11 from Germany, 10 from the Netherlands, 5 from USA, 5 from France, 2 from Denmark)	International Molecular Genetic Study of Autism, 1998
2q, 4q, 5p, 6q, 7q, 10q, 15q11-q15, 16p, 18q, 19p, Xp	<i>GABRB3</i> in 15q11-q15 region, <i>MACS</i> , <i>GRIK6</i> , <i>GPR6</i> in 6q region	51 families including at least two siblings or half-siblings affected by autism	Family	51 Caucasian families (18 from Sweden, 15 from France, 6 from Norway, 5 from the USA, 3 from Italy, 2 from Austria and 2 from Belgium)	Philippe et al., 1999
5p14.1	<i>CDH9</i> , <i>CDH10</i> in 5p14.1 region	943 families	Family	Autism Genetic Resource Exchange (AGRE)	Wang et al., 2009
5p14.1	<i>CDH9</i> and <i>CDH10</i> in 5p14.1 region	487 families	Family	487 Caucasian families (80 multiplex families, 407 singleton families)	Ma et al., 2009
5p15, 6q27, 20p13	<i>TAS2R1</i> and <i>SEMA5A</i> in 5p15 region	1031 multiplex families	Family	AGRE and US National Institute for Mental Health (NIMH)	Weiss et al., 2009
20p12.1	<i>MACROD2</i> in 20p12.1	1558 families	Family	Autism Genome Project (AGP)	Anney et al., 2010

Table 2 | Examples of ASD-associated human genetic variations.

Genes	CNV/SNV	Sample size	Design	Population	References
MET	rs1858830	743 autism families, 702 unrelated autism patients/189 unrelated controls	Case/control, family	Italian and American population	Campbell et al., 2007
WNT2	linkage disequilibrium in Wnt 3' UTR, R299W, L5R	75 autism-affected sibling pair families (ASP)	Trio	Families recruited from three regions of the United States (Midwest, New England, and mid-Atlantic states)	Wassink et al., 2001
	rs3779547, rs4727847, rs3729629	170 autism patients/214 normal controls	Case/control	Japanese population	Marui et al., 2010
RELN	5' UTR polymorphic GGC repeats	371 families	Family	Caucasian	Skaar et al., 2005
		172 autism trios, 95 unrelated autism patients/186 unrelated controls	Case/control, trio	Italian and American population	Persico et al., 2001
EN2/ ENGRAILED-2	rs1861972, rs1861973	518 families	Family	AGRE and National Institutes of Mental Health (NIMH)	Benayed et al., 2005; Gharani et al., 2004
HOXA1	A218G	57 probands, 166 relatives	Probands/relatives	Not identified	Ingram et al., 2000b
CHD8	<i>de novo</i> frameshift, nonsense mutations	209 trios	Trio	Simons Simplex Collection (SSC)	O'Roak et al., 2012a
GRIK2 (GluR6)	M867I	59 ASP, 107 trios	Family	Families recruited from 7 countries (Austria, Belgium, France, Italy, Norway, Sweden, US)	Jamain et al., 2002
GRM8	R859C, R1085Q, R1100Q, intrachromosomal segmental duplication	196 multiplex families	Family	AGRE	Serajee et al., 2003
GRIN2A (GluN2A)	rs1014531	219 sibling pairs, 32 families with extended relative pairs	Family	International Molecular Genetics Study of Autism Consortium (IMGSAC)	Barnby et al., 2005
GRIN2B (GluN2B)	<i>de novo</i> protein truncating and splicing mutations	209 trios	Trio	Simons Simplex Collection (SSC)	O'Roak et al., 2012a
GABRB3	Linkage disequilibrium	138 families, mainly trio	Family	104 Caucasian, 6 African American, 13 Asian American, 5 Hispanic	Cook et al., 1998
	Transmission disequilibrium	70 families	Trio	AGRE, Seaver Autism Research Center (SARC)	Buxbaum et al., 2002
5-HTT	Transmission disequilibrium	86 trios	Trio	68 Caucasian, 5 African American, 3 Hispanic American, 10 Asian American	Cook et al., 1997
TPH2	rs4341581, rs11179000	88 autistic subjects, 95 unrelated controls	Case/control	people from Utah	Coon et al., 2005

(Continued)

Table 2 | Continued

Genes	CNV/SNV	Sample size	Design	Population	References
NRXN1	rs1363036, rs930752, hemizygous CNV deletion of coding exons of NRXN1	1491 families	Family	Autism Genome Project (AGP) Consortium	Autism Genome Project et al., 2007
	L18Q, L748I, rs1045874	57 ASD subjects, 27 OCD subjects, 30 Tourette syndrome subjects	Case/control	Developmental Genome Anatomy Project (DGAP)	Kim et al., 2008
NLGN3	R451C	36 sibling pairs, 122 trios	Trio	not identified	Jamain et al., 2003
NLGN4	Frameshift mutation by 1bp insertion (1186InsT)				
SHANK1	<i>de novo</i> deletion	1614 ASD subjects, 15000 controls	Case/control	1158 Canadian, 456 European	Sato et al., 2012
SHANK2	CNV deletion for premature stop, R26W, P208S, R462X, T1127M, A1350T, L1008_P1009dup	396 ASD cases, 184 MR cases, 659 controls	Case/control	Canadian for ASD, German for MR	Berkel et al., 2010
	R443C, R598L, V717F, A729T, E1162K, G1170R, V1376I, D1535N, L1722P	851 ASD cases, 1090 controls	Case/control	Paris Autism Research International Sibpair (PARIS)	Leblond et al., 2012
SHANK3	R12C, A198G, R300C, G1011V, R1066L, R1231H, <i>de novo</i> frameshift mutation, <i>de novo</i> truncating mutation	227 families	Family	PARIS	Durand et al., 2007
CNTNAP2	rs2710102	476 trios	Trio	AGRE	Alarcon et al., 2008
	rs779475	72 families	Family	NIMH	Arking et al., 2008
	Nonsynonymous variants, I869T	635 patients, 942 controls	Case/control	587 white, 24 white-Hispanic, 7 unknown, 6 Asian, 6 more than one race, 3 African-American, 1 Native Hawaiian, 1 more than one race-Hispanic	Bakkaloglu et al., 2008
	rs17236239	184 families	Family	Specific Language Impairment Consortium (SLIC)	Vernes et al., 2008
ILRAPL1	Frameshift	142 ASD case, 189 controls	Case/control	85 French Canadians, 47 European Caucasians, 10 non-Caucasians	Piton et al., 2008
OPHN1	Frameshift				Piton et al., 2011
SYNGAP1	CNV deletion	996 ASD cases, 1287 controls	Case/control	European	Pinto et al., 2010
TM4SF2	Nonsynonymous variants, P172H	142 ASD case, 189 controls	Case/control	85 French Canadians, 47 European Caucasians, 10 non-Caucasians	Piton et al., 2011

same cell types in different species may have different functions. Moreover, the size, structural complexity, and neural connectivity of the human brain are much greater than those in rodent brains. These functional and anatomical differences between species may

create difficulties in translating the ASD-related mechanisms identified in model organisms into human applications. However, some fundamental aspects of the neural mechanisms identified in animal models such as alterations in synaptic transmission,

Table 3 | ASD models with chromosomal abnormality.

Mouse	Molecular function	Phenotype				Suggested mechanism	References
		Social interaction	Social communication	Repetitive behavior	Other phenotypes		
15q11-13 duplication	Ube3a, Gabr	Impaired	Reduced calls	Behavioral inflexibility	NA	Altered serotonergic signaling	Nakatani et al., 2009
16p11.2 CNV	Kif22, Mapk3	NA	NA	Climbing deficits	Altered diurnal rhythm	Hypothalamic Deficits	Horev et al., 2011
22q11.2 microdeletion	Dgcr2, Comt, Dgcr8	NA	NA	NA	Hyperactivity, Sensorygating deficits	Altered microRNA biogenesis	Stark et al., 2008

excitation-inhibition balance, and neuronal excitability might be conserved across species and translatable. In addition, given that stem cell technologies are rapidly improving, it is becoming easier for the changes observed in rodent neurons to be compared with those in human neurons derived from individuals with neuropsychiatric disorders (Brennand et al., 2011).

POTENTIAL MECHANISMS UNDERLYING ASD

Mechanisms underlying autism have been extensively studied using various approaches. Neuroanatomical studies have reported macrocephaly and abnormal neuronal connectivity in autistic individuals, while genetics studies using mouse models have implicated a variety of neuronal proteins in the development of ASD. More recently, defects in a number of synaptic proteins have been suggested to cause ASD via alterations in synaptic structure/function and neural circuits, suggesting that “synaptopathy” is an important component of ASD.

NEUROANATOMICAL ABNORMALITIES

A change frequently observed in the brains of individuals with ASD is the overgrowth of the brain termed macrocephaly, which is observed in ~20% of autistic children (Bolton et al., 2001; Courchesne, 2002; Courchesne et al., 2003, 2007; Fombonne et al., 1999; Hazlett et al., 2005). Aberrations in cytoarchitectural organization in autistic brains are observed during early brain development in regions including the frontal lobe, parieto-temporal lobe, cerebellum, and subcortical limbic structures (Fombonne et al., 1999; Bolton et al., 2001; Courchesne, 2002; Courchesne et al., 2003, 2007; Hazlett et al., 2005).

The cerebellum is a strong candidate for anatomic abnormalities in autism (Courchesne, 1997, 2002). Magnetic resonance imaging (MRI) studies have found hypoplasia of the cerebellar vermis and hemispheres, and autopsy studies have reported a reduction in the number of cerebellar Purkinje cells. In line with these anatomical changes, cerebellar activation is significantly reduced during selective attention tasks (Allen and Courchesne, 2003), whereas it is enhanced during a simple motor task (Allen et al., 2004). Although the putative role of the cerebellum in ASD has been restricted to sensory and motor dysfunctions, it is becoming increasingly clear that the cerebellum is associated with the core symptoms of autism.

In support of this notion, selective deletion of *Tsc1* (tuberous sclerosis 1) in cerebellar Purkinje cells is sufficient to cause all core autism-like behaviors in mice in association with reduced excitability in Purkinje cells (see also **Table 4** for summary of syndromic ASD models) (Tsai et al., 2012). In addition, mice lacking the neuroligin-3 gene (*Nlgn3*^{-/-} mice), another autism model with an *Nlgn3* deletion identified in autistic patients, show occluded metabotropic glutamatergic receptor (mGluR)-dependent long-term depression (LTD) at synapses between parallel fibers and Purkinje cells in association with motor coordination deficits (see also **Table 5** for summary of synaptopathy ASD models) (Baudouin et al., 2012). Both synaptic and behavioral perturbations are rescued by Purkinje cell-specific re-expression of *Nlgn-3* in juvenile mice, suggesting the interesting possibility that altered neural circuits can be corrected after completion of development.

The cerebral cortex is another brain region frequently affected in ASD. Abnormal enlargement or hyperplasia of the cerebral cortex has been reported in MRI studies on young children with ASD (Sparks et al., 2002; Herbert et al., 2003). Because frontal and temporal lobes are important for higher brain functions including social functioning and language development, these anatomical anomalies are likely to underlie the pathophysiology of autism.

The amygdala and hippocampus are subcortical brain regions associated with ASD (Aylward et al., 1999; Schumann et al., 2004; Schumann and Amaral, 2006). Some studies have reported that the autistic amygdala exhibits early enlargement, whereas others have reported a reduction in neuron numbers and amygdala volume. Increases and decreases in the volume of hippocampus are also associated with ASD.

Aberrant connectivity is an emerging theory to account for anatomical abnormalities in autism. Neuroimaging techniques, such as diffusion tensor imaging (DTI) and functional MRI (fMRI), have suggested that ASD involves abrogation of white matter tracts in brain regions associated with social cognition, such as the prefrontal cortex, anterior cingulate cortex, and superior temporal regions (Barnea-Goraly et al., 2004; Minshew and Williams, 2007). Alterations in connectivity across diverse brain regions associated with language, working memory, and social cognition have also been linked to autism. In general, it appears

Table 4 | Syndromic ASD models.

Mouse	Molecular function	Phenotype			Suggested mechanism	Potential therapeutics	Syndrome	References
		Social interaction	Social communication	Other phenotypes				
MeCP2 KO	Transcriptional regulator	Impaired (enhanced interaction)	Increased scent marking	Hindlimb clasping Respiratory problem, Lethality	Decreased GABAergic transmission	BDNF, IGF-1	Rett syndrome	Shahbazian et al., 2002; Moretti et al., 2005
FMR1 KO	Translational repressor	Impaired	NA	Hand flapping Learning deficits, Anxiety	mGluR hyperfunction	MPEP	FXS	Bernardet and Crusio, 2006
TSC1 HT, TSC1 ^{Cb} KO	Tumor suppressor	Impaired	Increased calls	Grooming, Behavioral inflexibility Ataxia	Cerebellar deficits	Rapamycin	Tuberous sclerosis	Auerbach et al., 2011; Tsai et al., 2012
TSC2 HT		Impaired	Increased calls	Increased marble burying Learning deficits	mGluR hypofunction	Rapamycin, CDPBB		Ehninger et al., 2008
NF1 HT	Tumor suppressor	Impaired	NA	Learning deficits	Ras signaling hyperactivation	NA	Neurofibromatosis	Costa et al., 2001, 2002
PTEN KO	Tumor suppressor	Impaired	NA	Learning deficits	PI3K pathway hyperactivation, Macrocephaly	NA	Cowden/Lhermitte-Duclos syndrome	Kwon et al., 2006
CNTNAP2 KO	Neuron-glia interaction, K ⁺ channel cluster	Impaired	Reduced calls	Grooming Seizure	Reduced number of interneurons, Abnormal neuronal migration	Risperidone	CDFE	Penagarikano et al., 2011
Scn1a KO	Na ⁺ channel	Impaired	NA	Grooming Seizure	Decreased GABAergic transmission	Clonazepam	Dravet's syndrome	Han et al., 2012

Table 5 | Synaptopathy ASD models.

Mouse	Molecular function	Phenotype			Suggested mechanism	Potential therapeutics	References
		Social interaction	Social communication	Other phenotypes			
NLGN1 KO	Synaptic adhesion molecule	Minimal impairment	NA	Grooming	NMDAR hypofunction	D-cycloserine	Blundell et al., 2010
NLGN2 Tg		Impaired	NA	Jumping	Increased GABAergic transmission	NA	Hines et al., 2008
NLGN3 R451C KI		Impaired	Increased calls	NA	Increased GABAergic transmission	NA	Tabuchi et al., 2007
NLGN3 KO		Impaired	Reduced calls	Normal behavioral flexibility	Decreased brain volume, Cerebellar deficit	NA	Radyushkin et al., 2009; Baudouin et al., 2012;
NLGN4 KO		Impaired, Less aggression	Reduced calls	Normal	Decreased brain volume	NA	Jamain et al., 2008
Shank1 KO	Synaptic scaffolding protein	Not impaired	Not impaired	Not impaired	Impaired glutamatergic transmission	NA	Hung et al., 2008; Silverman et al., 2011
Shank2 ^{exon7} KO		Impaired	Reduced calls, Pattern change	Grooming	NMDAR hyperfunction	NA	Schmeisser et al., 2012
Shank2 ^{exon6-7} KO		Impaired	Reduced calls	Jumping	NMDAR hypofunction	CDPPB, DCS	Won et al., 2012
Shank3 HT		Impaired	Reduced calls	NA	Impaired glutamatergic transmission	Ampakine, IGF-1	Bozdagi et al., 2010
Shank3B KO		Impaired	NA	Grooming	Striatal dysfunction	NA	Peca et al., 2011
Shank3 ^{exon4-9} KO		Impaired	Pattern change	Grooming	Impaired glutamatergic transmission	NA	Wang et al., 2011
Cadps2 KO	Ca ²⁺ -dependent secretion activating protein	Impaired, Maternal neglect	NA	NA	Decreased density of PV interneuron, Reduced BDNF release	BDNF	Sadakata et al., 2007
Syngap1 HT	GTPase-activating protein for Ras small GTPase	Normal social interaction, Impaired social recognition, Propensity toward social isolation	NA	Stereotypy (repeated single beam break within 1 s)	Premature spine maturation and hyperexcitability	NA	Guo et al., 2009; Clement et al., 2012

Table 6 | Non-synaptopathy ASD models.

Mouse	Molecular function	Phenotype			Suggested mechanism	Potential therapeutics	References	
		Social interaction	Social communication	Repetitive behavior				Other phenotypes
Dvl1 KO	Wnt signaling pathway	Impaired	Not impaired	NA	Sensory gating deficits	Impaired Wnt signaling	NA	Lijam et al., 1997; Long et al., 2004
Oxtr KO	Oxytocin receptor	Impaired, Less aggression	Reduced calls	Not impaired	NA	Impaired oxytocin signaling	Oxytocin	Takayanagi et al., 2005; Crawley et al., 2007
Engrailed-2 KO	Homeodomain transcription factor	Impaired	Not impaired	Not impaired	Learning deficits	Cerebellar deficits	NA	Brielmaier et al., 2012
Reeler	Extracellular matrix glycoprotein	Impaired, Increased social dominance	Reduced calls	NA	Learning deficits, Ataxia	Lissencephaly	Neonatal estrogen	Salinger et al., 2003; Lalonde et al., 2004
4E-BP2 KO	Translational control, mTOR downstream signal	Impaired	Increased call number and duration	Grooming, Increased marble burying	NA	Increased NLGNs translation, Increased excitation	4EGI-1 sh-NLGNs	Gkogkas et al., 2013
eIF4E O/E		Impaired	NA	Grooming, Increased marble burying	Impaired reversal learning, Impaired fear extinction	E/I imbalance in PFC, Increased LTP in striatum and hippocampus	4EGI-1	Santini et al., 2013

that autism subjects display local over-connectivity and long-range or inter-regional under-connectivity (Herbert et al., 2003, 2004; Baron-Cohen and Belmonte, 2005; Herbert, 2005; Just et al., 2007).

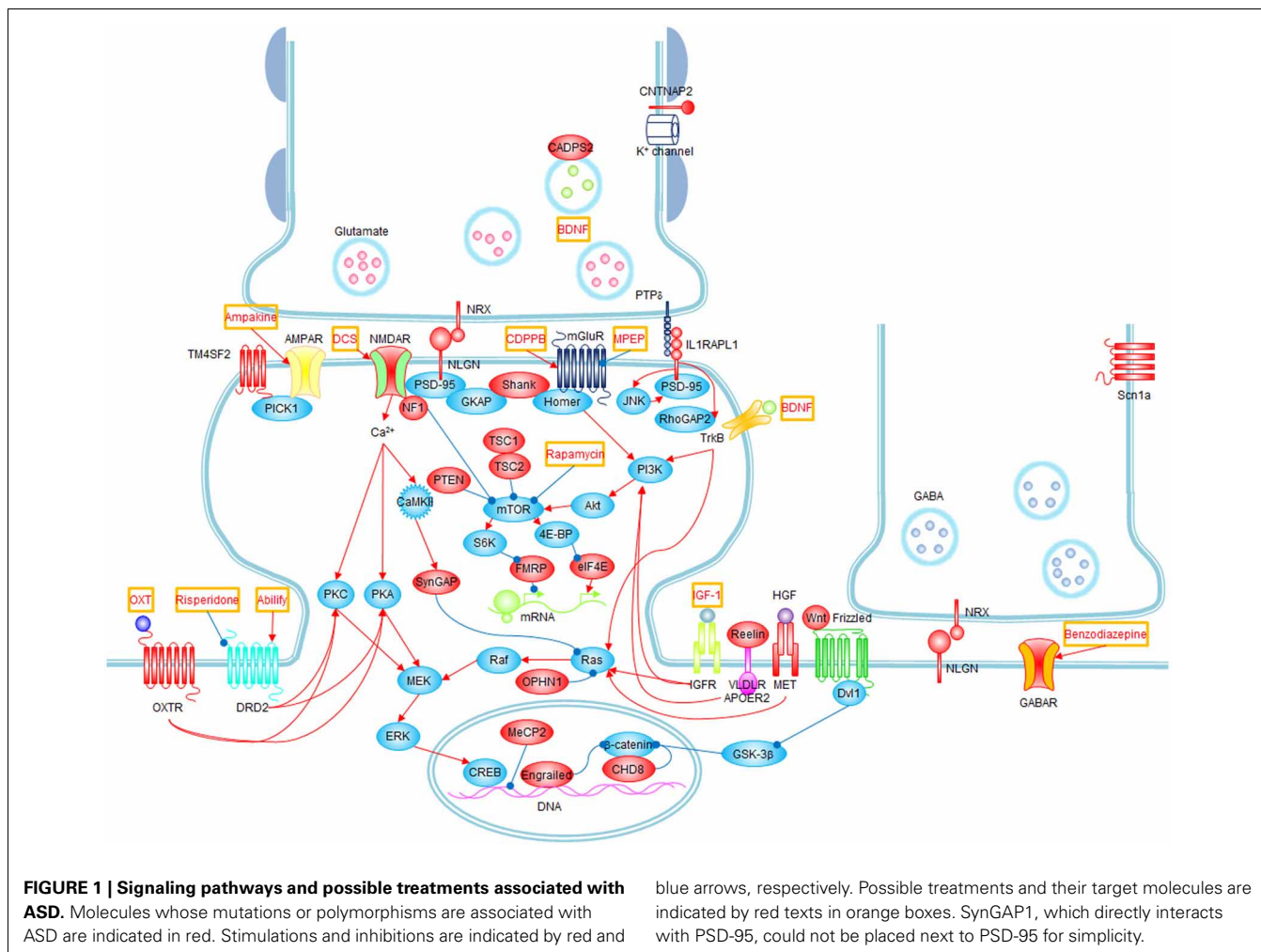
Potential ASD-related neural circuitries have also been proposed based on animal studies. *Shank3b*^{-/-} mice, which exhibit autistic-like behaviors, have striatal dysfunctions (Table 5) (Peca et al., 2011). In addition, a shift in the balance between excitation and inhibition (E-I balance) toward excitation in the mouse medial prefrontal cortex (mPFC) induced by optogenetic stimulation causes sociability impairments (Yizhar et al., 2011). These results suggest that the striatum and mPFC are components of ASD-related neural circuits.

Although various neuroanatomical defects are observed in autistic brains, a direct linkage between neuroanatomical anomalies and behavioral symptoms of ASD remains to be elucidated. Uncovering the detailed circuitries underlying autistic behaviors would help us understand higher cognitive functions, such as language and sociability.

EXTRACELLULAR FACTORS

It has been found that growth factors and neurotrophic factors are associated with ASD. Genetic and protein expression studies have shown that MET, a transmembrane receptor for hepatocyte growth factor (HGF) with tyrosine kinase activity, is associated with ASD. Genetic variations including rs1858830 in the promoter region that abrogate MET transcription are associated with ASD in Italian and American families and case/control studies, and the levels of MET mRNA and protein are reduced in the cortex of autistic patients (Campbell et al., 2007, 2006). However, this association between rs1858830 and ASD failed to replicate in another study (Sousa et al., 2009). By binding to MET, HGF acts as a neurotrophic factor for neurons to influence neurite outgrowth and dendritic morphology (Figure 1) (Powell et al., 2001, 2003; Sun et al., 2002; Gutierrez et al., 2004), implicating abnormal neuronal structures in ASD pathology.

WNT2 is a secreted growth factor that has been linked to ASD. Acting through the canonical Wnt pathway, WNT2 triggers a signal transduction cascade mediated by Dishevelled (Dvl1). WNT2 is a critical regulator of multiple biological functions, including embryonic development, cellular differentiation, and cell-polarity generation. It also regulates neuronal migration, axon guidance, and dendrite branching (Figure 1) (Logan and Nusse, 2004). Multiple lines of evidence have implicated the WNT2 locus in ASD: the WNT2 gene is located at the autism-susceptibility chromosomal locus 7q31 (Vincent et al., 2000; Warburton et al., 2000), and single nucleotide polymorphisms (SNP; rs3779547, rs4727847, and rs3729629, in a case/control study in a Japanese population) and several WNT2 locus variants (R299W and L5R, in autism-affected sibling pair [ASP] and trio families) are associated with autism (Wassink et al., 2001; Marui et al., 2010), although a subsequent study in Han Chinese trios failed to replicate the SNP association with ASD (Chien et al., 2011). While the majority of *Wnt2*^{-/-} mice are lethal (Goss et al., 2009), null mutants of *Dvl1* show deficits in nest building and home-cage huddling (see also Table 6 for summary



of non-synaptopathy ASD models) (Lijam et al., 1997; Long et al., 2004). Moreover, the Wnt signaling pathway is associated with and is regulated by chromodomain-helicase-DNA-binding protein 8 (CHD8; **Figure 1**), *de novo* mutations of which are repeatedly detected in autistic patients (Neale et al., 2012; O’Roak et al., 2012b; Sanders et al., 2012).

Brain-derived neurotrophic factor (BDNF) is associated with ASD. BDNF is a member of the neurotrophin family of growth factors that supports neurogenesis, axodendritic growth, neuronal/synaptic differentiation, and brain dysfunctions (**Figure 1**) (Huang and Reichardt, 2001; Martinowich et al., 2007). Elevated levels of BDNF were reproducibly found in the sera of Japanese and American autistic individuals (Connolly et al., 2006; Miyazaki et al., 2004). Another clue comes from calcium-dependent secretion activator 2 (CADPS2), a calcium binding protein in the presynaptic nerve terminal that interacts with and regulates exocytosis of BDNF-containing dense-core vesicles (**Figure 1**) (Cisternas et al., 2003). *CADPS2*, located at the autism-susceptibility locus on chromosome 7q31, is abnormally spliced in autism patients, and *Cadps2*^{-/-} mice exhibit social interaction deficits, including maternal neglect (**Table 5**) (Sadakata et al., 2007). Hence, although it is unclear how BDNF contributes to

autism pathogenesis, evidence for its role in ASD is becoming clear.

Reelin is also involved in autism. Reelin is a large secreted extracellular matrix glycoprotein that acts as a serine protease for the extracellular matrix, a function that is essential for neuronal migration, cortical patterning, and brain development (**Figure 1**) (Forster et al., 2006). The *RELN* gene is located in an autism susceptibility locus on chromosome 7q22, and triplet GGC repeats in 5’ untranslated regions (5’UTR) in the *RELN* gene have been associated with autism in a Caucasian population (Persico et al., 2001; Skaar et al., 2005) (**Table 2**). Expression levels of Reelin are decreased in postmortem autism brains (Fatemi et al., 2005). Reelin has also been implicated in pathogenesis of various neuropsychiatric disorders, including schizophrenia, bipolar disorder, lissencephaly, and epilepsy (Fatemi, 2001). Reeler mice, with a 150-kb deletion of the *Reln* gene, exhibit deficits in motor coordination, increased social dominance, and learning and memory impairments (**Table 6**) (Salinger et al., 2003; Lalonde et al., 2004).

TRANSCRIPTION FACTORS

Syndromic forms of ASD frequently involve transcription factors. This is likely because defective transcription factors have

significant influences on many genes and their downstream molecules, affecting diverse neuronal functions.

MeCP2 (X-linked gene methyl CpG binding protein 2) is one of the best examples. It is a member of a large family of methyl-CpG binding domain (MBD) proteins that selectively binds to methylated DNA and represses gene transcription (**Figure 1**) (Bienvenu and Chelly, 2006). Its downstream targets encompass ASD-related genes such as *BDNF* and *CDKL5*. Mutations in *MeCP2* are the major cause of Rett syndrome, a progressive neurodevelopmental disorder with autistic features (Amir et al., 1999; Bienvenu and Chelly, 2006; Chahrouh and Zoghbi, 2007). *Mecp2*-null mice, an animal model for Rett syndrome, recapitulate most symptomatic traits of Rett syndrome such as respiratory dysfunction, forelimb and hindlimb clasping stereotypy, motor dysfunction, tremor, hypoactivity, anxiety, cognitive impairments, and altered sociability (**Table 4**) (Shahbazian et al., 2002; Moretti et al., 2005).

Engrailed-2 is a homeodomain transcription factor associated with ASD. *Engrailed-2* is involved in a diverse range of biological processes from embryological development and segmental polarity to brain development and axon guidance (**Figure 1**) (Brunet et al., 2005; Joyner, 1996). The *Engrailed-2* gene on human chromosome 7q36 is in the autism susceptibility locus, and an association between two intronic SNPs rs1861972 and rs1861973 at *Engrailed-2* locus and ASD has been repeatedly identified in 518 ASD families (Gharani et al., 2004; Benayed et al., 2005) (**Table 2**). However, these SNPs were not found to be associated with ASD in Han Chinese trios (Wang et al., 2008). This association between *Engrailed-2* and ASD was further confirmed by animal model studies, which showed *Engrailed-2* null mice display social dysfunction and cognitive impairments (**Table 6**) (Briellmaier et al., 2012). Because *Engrailed-2* is expressed upon activation of WNT2-Dvl1 signaling, it appears that the WNT2-Dvl1-*Engrailed-2* pathway, which regulates neuronal migration and axonal guidance, may significantly contribute to ASD pathogenesis via neuroanatomical abnormalities. In addition, a base substitution (A218G) mutant of *HOXA1*, another homeobox gene, was reported in autistic individuals (Ingram et al., 2000b), indicating the importance of homeobox genes in normal brain function and ASD.

EXCITATORY AND INHIBITORY IMBALANCE

Mutations identified in important synaptic molecules including neuroligins (Jamain et al., 2003), neurexin (Autism Genome Project et al., 2007; Kim et al., 2008) and Shank (Durand et al., 2007; Berkel et al., 2010; Sato et al., 2012) in autistic subjects have prompted investigations into exploring the roles of synaptic dysfunctions in ASD pathogenesis. This “synaptopathy” model of autism has provided much insight into the field (**Table 5**).

Defects in synaptic proteins would lead to defective transmissions at excitatory and inhibitory synapses, disrupting the E-I balance in postsynaptic neurons, a key mechanism implicated in ASD. In line with this, ASD has been genetically associated with diverse glutamate receptors, including the kainite receptor subunit GluR6 (M867I in the intracytoplasmic C-terminal region of GluR6) (Jamain et al., 2002), the metabotropic glutamate receptor 8 (*GRM8*) (R859C, R1085Q, R1100Q, and intrachromosomal

segmental duplication) (Serajee et al., 2003), and the N-methyl-D-aspartic acid receptor (NMDAR) subunit GluN2A (rs1014531) (Barnby et al., 2005), and GluN2B (*de novo* protein truncating and splice mutations) (O’Roak et al., 2012a,b) (**Table 2**). Decreased levels of glutamine and abnormal levels of glutamate were observed in the plasma of autistic children (Rolf et al., 1993; Moreno-Fuenmayor et al., 1996). In addition, neuropathological studies of postmortem autism brains show perturbations in the glutamate neurotransmitter system (Purcell et al., 2001).

Abnormal GABAergic system is also proposed as a potential mechanism for ASD. Reduced expression levels in a rate-limiting enzyme for GABA synthesis, glutamic acid decarboxylase (GAD), and GABA receptors with altered subunit composition were observed in autistic brains (Fatemi et al., 2002, 2010). Furthermore, linkage disequilibrium and transmission disequilibrium between *GABRB3*, a gene encoding the $\beta 3$ subunit of GABA α receptors, with Angelman syndrome and autism has been reported (Cook et al., 1998; Bass et al., 2000; Buxbaum et al., 2002) (**Table 2**).

The serotonergic system would also play a role in ASD pathogenesis by modulating the E-I balance. Serotonin levels in blood or urine are increased in subjects with autism (Cook and Leventhal, 1996; Burgess et al., 2006), and various genes in the serotonin system are linked to autism. Among them are genes encoding the serotonin transporter 5-HTT (transmission disequilibrium at the 5-HTT locus in 86 autism trios) (Cook et al., 1997), and a rate-limiting enzyme for serotonin synthesis TPH2 (two intronic SNPs rs4341581 and rs11179000 at introns 1 and 4, respectively, have been associated with autism) (Coon et al., 2005) (**Table 2**).

Neurexins and neuroligins are synaptic cell adhesion molecules enriched at pre- and post-synaptic membranes, respectively (**Figure 1**) (Craig and Kang, 2007; Sudhof, 2008). Specific interactions between neurexins and neuroligins regulate various aspects of both excitatory and inhibitory synaptic development and function, affecting the E-I balance in postsynaptic neurons. Many mutations in genes encoding neurexins (including hemizygous CNV deletions and missense mutations) and neuroligins (e.g., R451C for *NLGN3* and a frameshift insertion mutation for *NLGN4*) have been associated with ASD, intellectual disability, and schizophrenia (Jamain et al., 2003; Laumonnier et al., 2004; Autism Genome Project et al., 2007; Kim et al., 2008; Walsh et al., 2008) (**Table 2**). *Neuroligin3* knockin mice with the R451C mutation found in autistic patients recapitulate autistic features including moderately impaired sociability (**Table 5**) (Tabuchi et al., 2007). Notably, inhibitory transmission was enhanced in the cortical regions of the mutant brains of these mutant mice, suggesting that disrupted E-I balance may contribute to ASD.

SHANK family genes encode scaffolding proteins enriched in the postsynaptic density (PSD), a postsynaptic membrane specialization composed of multi-synaptic protein complexes (**Figure 1**) (Sheng and Kim, 2000). The Shank family contains three known members, Shank1, Shank2 and Shank3, also known as ProSAP3, ProSAP1, and ProSAP2, respectively. The idea that Shanks are involved in the etiology of ASD firstly emerged

from Phelan-McDermid syndrome (PMS) or 22q13 deletion syndrome, a neurodevelopmental disorder caused by a microdeletion on chromosome 22 (Boeckers et al., 2002; Wilson et al., 2003; Phelan and McDermid, 2012). The association between *SHANK* and ASD became evident by identifying numerous mutations including *de novo* frameshift, truncating, and missense mutations on *SHANK3* locus in autistic individuals (Durand et al., 2007) (Table 2). Mutations in *SHANK2* and *SHANK1* including *de novo* CNV deletions and missense mutations in Canadian and European populations were also identified in individuals with ASD and intellectual disability (Berkel et al., 2010; Leblond et al., 2012; Sato et al., 2012).

Multiple lines of transgenic mice with *Shank* mutations found in human patients have been reported. *Shank3* heterozygous mice show sociability deficits and reductions in miniature excitatory postsynaptic currents (mEPSC) amplitude and basal synaptic transmission (Bozdagi et al., 2010); mice with deletion of exon 4–9 of *Shank3* are socially impaired and exhibit alterations in dendritic spine morphology and activity-dependent surface expression of AMPARs (Wang et al., 2011); *Shank1*^{-/-} mice display reduced basal synaptic transmission in the hippocampal CA1 region and reduced motor function and anxiety-like behavior, although they show normal sociability (Hung et al., 2008; Silverman et al., 2011); mice expressing *Shank2*-R462X in hippocampal CA1 neurons exhibit cognitive dysfunction accompanied by reduced mEPSC amplitude and changes in neuronal morphologies (Table 5) (Berkel et al., 2012).

CNTNAP2, a neuronal transmembrane protein, is a member of the neurexin family localized at juxtaparanodes of myelinated axons. Here, CNTNAP2 regulates neuron-glia interactions and potassium channel clustering in myelinated axons (Figure 1) (Poliak et al., 1999). Several SNPs (e.g., rs2710102, rs7794745, rs17236239) and nonsynonymous variants (e.g., I867T) in *CNTNAP2* locus were found to be associated with ASD, language impairment, and cortical dysplasia-focal epilepsy syndrome in humans (Alarcon et al., 2008; Arking et al., 2008; Bakkaloglu et al., 2008; Vernes et al., 2008) (Table 2). In a case-control association study in Spanish autistic patients and controls, however, *CNTNAP2* SNPs rs2710102 and rs7794745 did not associate with ASD (Toma et al., 2013). *Cntnap2*^{-/-} mice recapitulate all three core symptoms of autism, and display abnormal neuronal migration, reduced number of GABAergic interneurons, and abnormal neuronal synchronization (Table 4) (Penagarikano et al., 2011). Excessive grooming and hyperactivity in these mice were restored by the treatment of the antipsychotic risperidone (Table 4), suggesting the possibility of therapeutic intervention for certain symptoms of autism.

SynGAP is a GTPase-activating protein for the Ras small GTPase. SynGAP directly interacts with PSD-95, and negatively regulates the Ras-MAPK signaling pathway, excitatory synapse development, and synaptic transmission and plasticity (Figure 1) (Chen et al., 1998; Kim et al., 1998). In humans, *de novo* mutations of *SYNGAP1* have been associated with intellectual disability and autism (Hamdan et al., 2011). In addition, a genetic case/control study in European populations associates a rare *de novo* copy number variation in *SYNGAP1* with ASD (Pinto et al., 2010). *Syngap1* heterozygous

mice show schizophrenia-like phenotypes including hyperactivity, impaired sensory-motor gating, impaired social memory and fear conditioning, and preference to social isolation (Guo et al., 2009) (Table 5). In a more recent study, *Syngap1* heterozygous mice showed premature dendritic spine development together with enhanced hippocampal excitability and abnormal behaviors, suggesting that over-paced excitatory synaptic development during a critical time window of postnatal brain development causes intellectual disability and ASD (Clement et al., 2012).

Several genes associated with X chromosome-linked intellectual disability (XLID) and synaptic regulations have been associated with ASD. One of them is interleukin 1 receptor accessory protein-like 1 (*IL1RAPL1*) that encodes a synaptic transmembrane protein (Carrie et al., 1999). Recently, a systematic sequencing screen of X chromosomes of ASD-affected individuals has identified a *de novo* frameshift mutation in *IL1RAPL1* (Piton et al., 2008). *IL1RAPL1* plays an important role in the formation and stabilization of excitatory synapses by recruiting the scaffolding protein PSD-95 to excitatory postsynaptic sites through the JNK signaling pathway (Figure 1) (Pavlovsky et al., 2010). In addition, *IL1RAPL1* induces the presynaptic differentiation through its trans-synaptic interaction with protein tyrosine phosphatase δ (PTP δ) (Figure 1) (Valnegri et al., 2011b; Yoshida et al., 2011). This interaction between *IL1RAPL1* and PTP δ recruits RhoGAP2 to the excitatory synapses and induces dendritic spine formation (Valnegri et al., 2011b). Interestingly, *IL1RAPL1* regulates the development of inhibitory circuits in the cerebellum, an ASD-related brain region, and disrupts the excitatory and inhibitory balance, as determined by a study using *Il1rapl1*^{-/-} mice (Gambino et al., 2009). These results suggest that *IL1RAPL1* is involved in the regulation of excitatory synaptic development and the balance between excitatory and inhibitory synaptic inputs.

Another XLID gene related with ASD is *OLIGOPHRENIN-1* (*OPHN1*), which encodes a GTPase-activating protein that inhibits Rac, Cdc42, and RhoA small GTPases. Since the initial report of the association of a truncation mutation of *OPHN1* with XLID (Billuart et al., 1998a,b), additional studies have associated nonsynonymous rare missense variants in *OPHN1* with ASD (e.g., H705R) and schizophrenia (e.g., M461V) (Piton et al., 2011). *OPHN1* regulates dendritic spine morphogenesis through the RhoA signaling pathway (Govek et al., 2004) and activity-dependent synaptic stabilization of AMPA receptors (Nadif Kasri et al., 2009). *OPHN1* also interacts with the transcription repressor Rev-erba to regulate expression of circadian oscillators (Valnegri et al., 2011a). Importantly, *Ophn1*^{-/-} mice show immature spine morphology, impaired spatial memory and social behavior, and hyperactivity (Khelifaoui et al., 2007). These results suggest that *OPHN1* regulates excitatory synaptic development and function.

TM4SF2 or *tetraspanin 7* (*TSPAN7*), another X-linked gene which encodes a membrane protein which belongs to transmembrane 4 superfamily (TM4SF), plays important roles in the cell proliferation, activation, growth, adhesion, and migration (Maecker et al., 1997). TM4SF proteins form a complex with integrin, which regulates cell motility and migration by modulating

the actin cytoskeleton (Berdichevski and Odintsova, 1999). A balanced translocation and mutations (a nonsense mutation and a P172H missense mutation) of *TM4SF2* was firstly discovered in the individuals with XLID (Zemni et al., 2000). In subsequent studies, the P172H missense mutation was found in individuals with XLID (Maranduba et al., 2004) and ASD (Piton et al., 2011). A microduplication in the locus of *TM4SF2* was revealed, but this duplication was also present in unaffected controls, suggesting that it may be a neutral polymorphism (Cai et al., 2008). In neurons, *TM4SF2* regulates excitatory synaptic development and AMPA receptor trafficking by binding to the synaptic PDZ protein PICK1 (Figure 1) (Bassani et al., 2012).

SYNAPTIC SIGNALING

Disrupted synaptic signaling may be a key determinant of ASD. Components in mGluR- or NMDAR-dependent signaling cascades have recently been implicated in ASD.

Neurofibromin 1 (*NF1*), tuberous sclerosis complex (*TSC1/TSC2*), and phosphatase and tensin homolog (*PTEN*) are genes associated with neurological diseases with common autistic symptoms including neurofibromatosis (Rasmussen and Friedman, 2000), tuberous sclerosis (van Slegtenhorst et al., 1997), and Cowden/Lhermitte-Duclos syndrome (Pilarski and Eng, 2004). They are tumor suppressors sharing a common function; they negatively regulate the mammalian target of rapamycin (mTOR) signaling pathway. Although *Tsc1* null mice are embryonically lethal (Wilson et al., 2005), mutant mice with loss of *Tsc1* in cerebellar Purkinje cells display autistic-like behaviors (Tsai et al., 2012), and *Tsc2* heterozygote mice exhibit abnormal social communication (Young et al., 2010); *Nf1* mutant mice show aberrant social transmission of food preference and deficits in hippocampus-dependent learning (Costa et al., 2001, 2002); *Pten* deficient mice show altered social interaction and macrocephaly with hyperactivation of mTOR pathway (Table 4) (Kwon et al., 2006).

Signaling molecules in the downstream of mTOR in the mTOR pathway play crucial roles in ASD pathogenesis. Upon phosphorylation by mTORC1, 4E-BP proteins are detached from eIF4E to promote eIF4E-dependent protein translation (Figure 1) (Richter and Sonenberg, 2005). A SNP at eIF4E promoter region which increases its promoter activity was found in autism patients (Neves-Pereira et al., 2009). Implications of mTOR downstream signaling in ASD were demonstrated as 4E-BP2 knockout mice and eIF4E overexpression mice display autistic-like behaviors. 4E-BP2 knockout mice show enhanced translational control of neuroligins and increased excitatory transmission in the hippocampus (Table 6) (Gkogkas et al., 2013), while eIF4E overexpressing transgenic mice show impaired excitatory/inhibitory balance in the mPFC and increased LTD in the hippocampus and striatum (Table 6) (Santini et al., 2013). Autistic features of these mutant mice were ameliorated by 4EGI-1 infusion, which inhibits the eIF4E–eIF4G interaction.

Fragile X syndrome is the most common cause of intellectual disability and autism. It is mostly caused by the expansion of CGG trinucleotide repeats in the promoter region of the *FMR1* gene, which enhances the methylation of the promoter and represses generation of *FMR1*-encoded protein (FMRP),

which binds to target mRNAs and regulates their translation and transport of mRNA into dendrites and synapses (Figure 1) (Bassell and Warren, 2008). In the absence of FMRP, target mRNA translation becomes excessive and uncontrolled, leading to an aberrant activity-dependent protein synthesis. *Fmr1* mutant mice show enhanced protein synthesis-dependent mGluR-mediated LTD and dendritic spine elongation, together with cognitive deficits, social anxiety and impaired social interaction (Table 4) (Bernardet and Crusio, 2006). Interestingly, target molecules of FMRP include Shank3, GluN2A, mTOR, TSC2, NF1, neuroligin2, and neurexin1 (Darnell et al., 2011), which are associated with ASD pathogenesis.

It should be noted that the ASD-related signaling molecules mentioned above are also associated with NMDAR and mGluR signaling pathways. NMDARs and mGluRs play critical roles in the regulation of synaptic function and plasticity at excitatory synapses. NF1 interacts with the NMDAR complex and regulates GluN2A phosphorylation (Figure 1) (Husi et al., 2000). FMRP and TSC have profound effects on mGluR-dependent LTD and protein synthesis, which are upregulated in *Fmr1*^{-y} mice, while downregulated in *Tsc2*^{+/-} mice (Auerbach et al., 2011). FMRP is also in the downstream of mGluR signaling (Figure 1) (Bassell and Warren, 2008).

Defects in NMDAR function and associated signaling are also observed in nonsyndromic ASD models with *Shank* mutations. Shank proteins are physically connected to both NMDARs and mGluRs, suggesting that Shank may regulate signaling pathways downstream of NMDAR or mGluR activation, and the functional interaction between the two receptors (Figure 1). *Shank2*^{-/-} mice with the deletion of exons 6 and 7 display autistic-like behaviors and reductions in NMDAR function and associated signaling, without affecting mGluR-dependent LTD (Won et al., 2012), while *Shank2*^{-/-} mice with exon 7 deletion show similar behavioral abnormalities with NMDAR hyperfunction (Table 5) (Schmeisser et al., 2012). Although how similar exon deletions in *Shank2* lead to comparable behavioral abnormalities but different changes in NMDAR function remains to be determined, these results point to that Shank2 is an important regulator of NMDAR function, and that NMDAR function and NMDAR-associated signaling are associated with ASD.

NEUROIMMUNE RESPONSE

The implication of the immune system on autism was initially proposed in 1976 based on that some autistic children do not have detectable Rubella titers in spite of previous vaccination (Stubbs, 1976). Levels of serum IgG and autoantibodies to neuronal and glial molecules were elevated in autistic patients (Singh et al., 1997; Croonenberghs et al., 2002), proposing involvement of autoimmune responses in autism. In addition, plasma or cerebrospinal fluid (CSF) levels of pro-inflammatory cytokines and chemokines including MCP-1, IL-6, IL-12, IFN- γ and TGF β 1 were increased in autistic individuals (Ashwood and Van de Water, 2004; Ashwood et al., 2006).

Astrocytes and microglia are two glial cell types important for immune responses in the brain as well as regulation of neuronal functions and homeostasis (Fields and Stevens-Graham, 2002). Postmortem analyses demonstrated abnormal glial activation and

neuroinflammatory responses in autistic brains (Vargas et al., 2005). Transcriptome analysis of autistic postmortem brain tissues has also revealed upregulation in the expression of genes belonging to immune and inflammatory networks (Voineagu et al., 2011). Reactive astrocytes were also detected in *Cntnap2*^{-/-} brains, a well-established autism model (Penagarikano et al., 2011). These results clearly suggest the association between neuroimmune defects with ASD, although further details remain to be determined.

NON-GENETIC MODELS OF ASD

Although we have thus far described genetic factors underlying ASD, environmental factors also have strong influences on ASD. Epidemiologic studies suggest that maternal exposure to stress, viral or bacterial infection, thalidomide, and valproic acid can increase the risk for ASD in offspring (Grabrucker, 2012).

Maternal immune activation (MIA) induced by poly(I:C), the synthetic doublestrand RNA polyribonucleosinic-polyribocytidilic acid, in pregnant mice leads to the development of core ASD-like phenotypes in the offspring, including impaired sociability, decreased USV, and increased repetitive behaviors (Malkova et al., 2012). MIA by lipopolysaccharide (LPS) treatment during pregnancy can also induce ASD-like phenotypes in rodent offspring, including impaired social interaction (Hava et al., 2006; Kirsten et al., 2010) and reduced USV (Baharoori et al., 2012). IL-6 is thought to play a critical role in this process, as IL-6 knockout mice do not show poly(I:C) induced social deficits (Smith et al., 2007), and IL-6 levels are significantly elevated in the cerebellum of autistic subjects (Wei et al., 2011). Although further details remain to be determined, the underlying mechanisms may include IL6-dependent regulation of excitatory and inhibitory synaptic transmission and neuroprotection (Sallmann et al., 2000; Biber et al., 2008; Dugan et al., 2009).

Prenatal exposure to teratogens can increase the risk for ASD in animals, as in humans. Thalidomide (THAL) and valproic acid (VPA) cause rat offspring to display brain morphological abnormalities observed in ASD, including altered cerebellar structures and reduced number of cranial motor neurons (Rodier et al., 1997; Ingram et al., 2000a). Behaviorally, VPA-exposed rats show decreases in prepulse inhibition, stereotypy, and social behaviors (Schneider and Przewlocki, 2005). VPA-exposed rats display elevated serotonin levels and abnormal serotonergic neurons (Anderson et al., 1990; Narita et al., 2002; Miyazaki et al., 2005), decreased parvalbumin-positive interneurons in the neocortex (Gogolla et al., 2009), and elevated NMDA receptor levels and enhanced LTP (Rinaldi et al., 2007), suggesting that these mechanisms may contribute to the development of ASD-like phenotypes.

POTENTIAL TREATMENTS FOR ASD

Currently, only two medicines have been approved for ASD by US FDA; risperidone (Risperdal®) and aripiprazole (Abilify®), which act as dopamine/5-HT receptor antagonists (McPheeters et al., 2011). These drugs are useful for correcting irritability and stereotypy, but not sociability defects. Recently, a number of candidate ASD medications for treating social abnormalities have been suggested (Figure 1).

mGluR POSITIVE ALLOSTERIC MODULATORS

mGluR1 and mGluR5 are group I mGluRs that are postsynaptically expressed in broad brain regions, including the cerebral cortex, striatum, hippocampus, nucleus accumbens, and inferior colliculus (Testa et al., 1995). Upon activation, group I mGluRs enhance calcium release from intracellular stores resulting in neuronal depolarization, augmentation of neuronal excitability, and activation of intracellular signaling cascades such as PKA, PKC, MAPK, ERK, and CREB (Niswender and Conn, 2010). mGluR5 is physically linked to NMDARs via Homer-Shank/ProSAP-GKAP/SAPAP-PSD-95 interactions (Naisbitt et al., 1999; Tu et al., 1999), and is functionally coupled to NMDARs via aforementioned signaling molecules including PKC (Niswender and Conn, 2010). Through these structural and biochemical interactions, mGluR5 activation is thought to potentiate NMDAR function (Awad et al., 2000; Attucci et al., 2001; Mannaioni et al., 2001; Pisani et al., 2001; Alagarsamy et al., 2002; Rosenbrock et al., 2010).

Positive allosteric modulators of mGluR5 receptors were first developed to alleviate symptoms of schizophrenia (Gregory et al., 2011). Although antipsychotics are available for positive symptoms of schizophrenia, such as hallucinations, no medications are currently available for negative symptoms or cognitive impairments. Two main hypotheses have been proposed for schizophrenia: dopaminergic hyperactivity and NMDA hypofunction. Dopaminergic hyperactivity can be treated by dopamine receptor-antagonistic antipsychotics such as risperidone, but NMDA hypofunction is difficult to modulate given the expected side effects of enhancing NMDAR functions.

Therefore, the concept of augmenting NMDAR signaling via mGluR potentiation was proposed to improve negative symptoms of schizophrenia (Uslaner et al., 2009; Stefani and Moghaddam, 2010). mGluR positive allosteric modulators increase the function of NMDAR only when they are occupied by the endogenous ligand glutamate (Figure 1). mGluR positive allosteric modulators have significant advantages over the conventional mGluR agonist, (RS)-3,5-dihydroxyphenylglycine (DHPG). While DHPG has poor specificity toward particular mGluR subtypes, mGluR positive allosteric modulators offer high subtype specificity. Some positive allosteric modulators have high brain blood barrier penetrance, which enables the systemic administration of the drugs. Furthermore, whereas direct mGluR agonists cause rapid receptor desensitization, mGluR positive allosteric modulators potentiate mGluR function with minimal desensitization, because they bind to an allosteric site on the receptor distinct from the orthosteric glutamate binding site. These properties of positive allosteric modulators are predicted to minimize their excitotoxicity and enable high-dose administrations.

A large number of mGluR5 allosteric modulators have been developed (Williams and Lindsley, 2005; Gregory et al., 2011). Of these, CDPPB, ADX47273, MPPA, and VU0092273 readily cross the blood-brain barrier, and CDPPB, particular, has been examined in various behavioral assays and model animals. In CHO (Chinese hamster ovary) cells expressing human mGluR5, CDPPB treatment was shown to enhance mGluR5 activity in a concentration-dependent manner (Kinney et al.,

2005). Behaviorally, CDPPB alleviates prepulse inhibition and hyperactivity produced by amphetamine, suggesting that CDPPB could be a potential antipsychotic agent.

Because NMDARs play an essential role in learning and memory, indirect potentiation of NMDARs by mGluR5 positive allosteric modulators may facilitate synaptic plasticity and learning and memory. Indeed, CDPPB and ADX47273 enhance the performance of wild-type mice in the Morris water maze test, a hippocampus-dependent learning and memory paradigm (Ayala et al., 2009). In addition, VU-29 and ADX47273 potentiate two forms of NMDAR-dependent synaptic plasticity—LTP and LTD—in the CA1 region of the hippocampus (Ayala et al., 2009). DFB-treated rats make fewer errors in the Y-maze spatial alternation task (Balschun et al., 2006), and CDPPB and ADX47273 enhance performance in novel object recognition and five-choice serial reaction time tasks (Liu et al., 2008; Uslaner et al., 2009). CDPPB not only improves learning and memory performance of wild-type mice, but also reverses cognitive dysfunction and behavioral inflexibility induced by the NMDAR antagonist MK-801 (Uslaner et al., 2009; Stefani and Moghaddam, 2010). These results suggest that mGluR5 positive allosteric modulators have the potential to improve cognitive impairments associated with brain disorders including schizophrenia and autism.

Indeed, CDPPB has recently shown promise as a potential treatment for ASD. In a study using *Tsc2*^{+/-} mice, a mouse model of tuberous sclerosis characterized by intellectual disability and autism, Mark Bear and colleagues showed that cognitive impairments observed in these mice could be alleviated by CDPPB administration (Table 4) (Auerbach et al., 2011). In addition, social deficits of *Shank2*^{-/-} mice are rescued by CDPPB treatment (Won et al., 2012), implicating hypofunction of mGluRs and NMDARs in social impairment, and suggesting mGluR positive allosteric modulators as novel therapeutics for the treatment of social deficits (Table 5). More recently, CDPPB was shown to reverse defects in social novelty recognition induced by neonatal phencyclidine treatment (Clifton et al., 2012).

D-CYCLOSERINE

Although it is well established that NMDARs critically regulate normal brain functions, the excitotoxicity and poor bioavailability of direct NMDAR agonists have hampered attempts to control brain activity by modulating NMDARs (Quartermain et al., 1994). D-cycloserine is a high-affinity partial agonist of NMDA-coupled, strychnine-insensitive glycine receptors (Figure 1) (Hood et al., 1989). Similar to glycine, D-cycloserine also binds to the glycine site of NMDARs as a partial agonist, potentiating NMDARs by increasing the frequency of channel opening. In addition, because NMDARs are not maximally potentiated by endogenous glycine, there is room for D-cycloserine to further potentiate NMDARs. These properties enable D-cycloserine to act as a positive modulator of NMDARs.

D-cycloserine is a viable drug candidate because it is a partial agonist, displaying efficacy of 40–50% relative to glycine, and has low toxicity and decent bioavailability (Hood et al., 1989). Although the brain penetrance of D-cycloserine is not high, it can nonetheless infiltrate the blood-brain barrier, exerting a peak

effect 1 h after intraperitoneal administration (Peterson, 1992). D-cycloserine shows dose-dependent elimination (higher elimination rates with lower doses) and a half-life of 7–15 h in humans and 23 min in mice (Iwainky, 1988; Wlaz et al., 1994).

When glycine levels are low, D-cycloserine amplifies the activity of the NMDAR complex and enhances synaptic plasticity and cognitive function. D-cycloserine alleviates senescence-associated behavioral defects (Flood et al., 1992) and facilitates memory acquisition, consolidation, and retrieval (Quartermain et al., 1994). While low doses (10–20 mg kg⁻¹) of D-cycloserine have cognition-enhancing effects (Monahan et al., 1989; Flood et al., 1992; Schuster and Schmidt, 1992; Sirvio et al., 1992; Quartermain et al., 1994), higher doses (>100 mg kg⁻¹) exert anticonvulsant effects in tonic convulsion models (Peterson, 1992; Peterson and Schwade, 1993).

Putative effects of D-cycloserine on ASD have been suggested by previous studies. Mice with a *neuroligin1* (*Nlgn1*) deficiency exhibit abnormally increased grooming behavior, and this behavioral anomaly is reversed by D-cycloserine treatment (Table 5) (Blundell et al., 2010). Low-dose D-cycloserine alleviates negative symptoms of schizophrenia-affected individuals (Goff et al., 1999), and reduces social withdrawal and increases social responsiveness in autistic patients (Posey et al., 2004). Moreover, D-cycloserine partially rescues social deficits of *Shank2*^{-/-} mice, supporting the role of NMDAR functionality in autism (Table 5) (Won et al., 2012).

BENZODIAZEPINES

Recently, benzodiazepines were suggested as putative therapeutic agents for Dravet's syndrome, which is a developmental disorder with myoclonic infantile seizure, ADHD-like inattention and hyperactivity, motor impairment, sleep disorder, anxiety-like behaviors, cognitive defects, autism-like social dysfunction, and restricted interests. Mice heterozygous for a deletion of the α -subunit of the type 1 voltage-gated sodium channel (*Scn1a*^{+/-} mice), an animal model for Dravet's syndrome, recapitulate most features of the disorder, including epilepsy, ataxia, sleep disorder, anxiety-like behaviors, hippocampus-dependent learning impairments, sociability deficits, and excessive repetitive grooming behaviors (Table 4) (Yu et al., 2006; Kalume et al., 2007; Han et al., 2012). In *Scn1a*^{+/-} mouse brains, expression of the voltage-gated sodium channel type-1 (Na_v1.1) is decreased in GABAergic interneurons, and GABAergic transmission onto postsynaptic neurons was reduced. This would cause a shift in the balance between excitation and inhibition in postsynaptic neurons toward excitation, which may be corrected by stimulating GABA receptors in these neurons. Indeed, it was shown that both behavioral abnormalities and aberrant GABAergic transmission are rescued by low-dose administration of clonazepam (Table 4) (Han et al., 2012).

Clonazepam, a type of benzodiazepine, is a positive allosteric modulator of GABA_A receptors that exerts sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxing effects (Figure 1) (Rudolph and Knoflach, 2011). Similar to the action of mGluR positive allosteric modulators, clonazepam potentiates GABA signaling only when GABA_A receptors are bound by their endogenous ligand, GABA. Therefore, these results indicate that

normalization of disrupted E-I balance may be a novel and promising strategy for treating symptoms of ASD.

mGluR NEGATIVE ALLOSTERIC MODULATORS

The potential of mGluR of negative allosteric modulation as a therapeutic strategy in ASD was first proposed based on studies in *Fmr1*^{-/-} mice, an animal model for fragile X syndrome (Bakker et al., 1994). The enhanced mGluR5-dependent LTD and protein synthesis observed in *Fmr1*^{-/-} mice provided a conceptual framework for the mGluR theory of fragile X pathogenesis (Bear et al., 2004; Bassell and Warren, 2008). Synaptic protein synthesis is stimulated by local mRNA translation, a process that depends on group I mGluR activation. FMRP, encoded by the *Fmr1* gene, is a repressor of mRNA translation; thus, mGluR-mediated protein synthesis could be enhanced in the absence of FMRP. Therefore, attempts have been made to correct fragile X syndrome by suppressing abnormally enhanced mGluR5-dependent synaptic plasticity and protein synthesis.

Two approaches have been used to normalize behavioral and neuronal deficits of *Fmr1*^{-/-} mice: genetic crossbreeding with *Tsc2*^{+/-} mice, which exhibit suppressed mGluR activity, and acute administration of an mGluR antagonist (Auerbach et al., 2011). Administering the mGluR5 antagonist 2-methyl-6-(phenylethynyl) pyridine hydrochloride (MPEP) to *Fmr1*^{-/-} mice normalizes defective phenotypes, including cognitive deficits, perturbed mGluR-dependent LTD and protein synthesis, and excessive filopodia-like long and thin spines (Figure 1, Table 4) (Yan et al., 2005; de Vrij et al., 2008). In line with this, mGluR negative allosteric modulators are now in clinical trials for fragile X syndrome patients (Krueger and Bear, 2011).

The therapeutic potential of mGluR antagonists in ASD has also been suggested. Repetitive grooming behaviors in BTBR and valproic acid (VPA) mouse models of autism are significantly alleviated by MPEP treatment (Silverman et al., 2010a; Mehta et al., 2011). Impairments in social interaction of BTBR mice are also ameliorated by MPEP administration (Silverman et al., 2010a). GRN-529, a selective negative allosteric modulator of mGluR5 developed by Pfizer, was shown to fully rescue excessive repetitive grooming behavior and social dysfunction in BTBR mice and jumping stereotypy in C58/J mice (Silverman et al., 2012). These findings suggest that mGluR negative allosteric modulators have novel therapeutic potential in autism, in addition to fragile X syndrome.

NMDAR ANTAGONISTS

NMDAR antagonists including amantadine and its close analogue memantine are now in clinical trials for autistic patients (Nightingale, 2012; Spooen et al., 2012). Amantadine and memantine are non-competitive antagonists for NMDARs with multiple clinical uses (Chen et al., 1992; Blanpied et al., 2005). Memantine is currently being used for Alzheimer's disease, while it is also useful for viral infection and Parkinson's disease. Because both drugs are weak NMDAR antagonists with moderate affinity, prolonged receptor blockade during treatment is unlikely to cause significant side effects.

In a double-blind, placebo controlled study, amantadine-treated group show significant improvements in hyperactivity

and inappropriate speech (King et al., 2001). Memantine is also effective in improving language and social behavior and clinical global impressions (CGI) scale in autistic patients (Chez et al., 2007; Erickson et al., 2007; Niederhofer, 2007).

With regard to mechanisms of memantine and amantadine underlying the treatment of ASD remains, both medications are highly likely to exert their therapeutic effects by suppressing NMDAR function and modulating excitotoxicity in autistic subjects. However, care should be taken because other possibilities exist. For instance, memantine treatment promotes excitatory synapse formation and maturation and cell adhesion properties of cerebellar granule cells (CGCs) of *Fmr1* knockout mice (Wei et al., 2012). In addition, memantine exerts neuroprotective activities by promoting glia-derived neurotrophic factor (GDNF) release and preventing microglial inflammatory responses (Wu et al., 2009). Memantine can also act as a non-competitive antagonist for 5-HT receptors (Rammes et al., 2001) and nicotinic acetylcholine receptors (Aracava et al., 2005), while it functions as an agonist for D2 dopamine receptors (Seeman et al., 2008).

IGF-1

A new approach for alleviating phenotypic traits of ASD in animal models has come from research on Rett syndrome. Rett syndrome is an X-linked neurological disorder caused by mutations in the *MeCP2* gene. MeCP2 is a transcriptional repressor and activator, which binds widely across the genome and influence a large number of genes (Chahrouh et al., 2008). One of the best characterized targets of MeCP2 is BDNF, a neurotrophic factor that regulates neuronal development and synaptic plasticity (Figure 1) (Greenberg et al., 2009). *Bdnf* conditional knockout mice show features analogous to Rett syndrome, including smaller brain size and hindlimb-clasping behavior (Chang et al., 2006). Mice with double knockout of *Bdnf* and *MeCP2* show earlier onset of Rett-like symptoms, whereas overexpression of *Bdnf* in *MeCP2* knockout mice delays the onset and relieves the electrophysiological defects of *MeCP2* mutants. Moreover, restoring *Bdnf* expression through ampakine administration alleviates respiratory problems of *MeCP2* mutant mice (Ogier et al., 2007). Although BDNF appears to have significant effects in Rett syndrome model animals, it poorly penetrates the blood-brain barrier, limiting its therapeutic application.

Another growth factor associated with Rett syndrome is insulin-like growth factor 1 (IGF-1) (Figure 1). IGF-1 is a polypeptide hormone with structural similarity to insulin. While it has a profound effect on overall cell growth, it also plays an important role in regulating neuronal functions by promoting axonal outgrowth (Ozdinler and Macklis, 2006), neuro- and synaptogenesis (O'Kusky et al., 2000), and activity-dependent cortical plasticity (Tropea et al., 2006). IGF-1 binds to IGF-binding proteins (IGFBP1–6), resulting in extension of the half-life of IGF-1 (Hwa et al., 1999). Upon binding to its cognate receptor, IGF-1 activates Ras-MAPK and PI3K-Akt pathways (Fernandez and Torres-Aleman, 2012), signaling cascades that are also activated by BDNF.

Because IGF-1 crosses the blood-brain barrier, it may be a viable alternative to BDNF as a therapeutic agent for Rett

syndrome. Indeed, IGF-1 and IGFBP have been implicated in Rett syndrome and autism: IGFBP3 levels are abnormally elevated in *MeCP2* mutant mice and Rett syndrome patients (Itoh et al., 2007), and the concentration of IGF-1 in CSF is reduced in autistic individuals (Riikonen et al., 2006). The therapeutic utility of IGF-1 in Rett syndrome was originally suggested by Mriganka Sur and coworkers, who reported that lethality, hypoactivity, and respiratory problems of *MeCP2*-null mice are partially rescued by IGF-1 treatment in association with normalization of impaired spine density, synaptic transmission, and cortical plasticity (Table 4) (Tropea et al., 2009). IGF-1 also reverses the reduction in excitatory synapse number and density of neurons derived from Rett patients (Marchetto et al., 2010).

RAPAMYCIN

Rapamycin is an immunosuppressant originally identified as an antifungal agent in isolates from *Streptomyces hygroscopicus* (Sehgal et al., 1975; Vezina et al., 1975; Baker et al., 1978; Singh et al., 1979). Rapamycin strongly binds to FK506-binding protein (FKBP); this complex then binds and inhibits mTOR, a serine/threonine kinase implicated in transcription, cytoskeleton dynamics, ubiquitin-dependent protein degradation, autophagy, and membrane trafficking (Figure 1) (Dennis et al., 1999). mTOR signaling has profound effects on neuronal cells in addition to cancer cells (Busaidy et al., 2012), immune cells (Araki et al., 2011), and cells that regulate lifespan (Powers et al., 2006; Harrison et al., 2009). In the nervous system, mTOR regulates axon guidance, dendrite arborization, synaptogenesis, and synaptic plasticity (Troca-Marin et al., 2012).

Perturbations in mTOR signaling have significant impacts on normal brain functions. Patients with Alzheimer's disease and *Drosophila* tauopathy models show enhanced mTOR signaling in the brain (Li et al., 2005; Khurana et al., 2006). Hyperactivation of the Akt-mTOR pathway is observed in hippocampal neurons of *Ts1Cje* mice, which models Down syndrome (Troca-Marin et al., 2011). Animal models and patients of Parkinson's disease exhibit enhanced levels of REDD1, which inhibits mTOR activity (Malagelada et al., 2006). mTOR is observed in inclusion bodies from Huntington's disease patients and corresponding mouse models (Ravikumar et al., 2004). Importantly, rapamycin treatment alleviates several pathogenic traits observed in *in vivo* and *in vitro* models of Alzheimer's disease (Khurana et al., 2006; Harrison et al., 2009), Parkinson's disease (Pan et al., 2009; Tain et al., 2009), and polyglutamine diseases (Ravikumar et al., 2004; Berger et al., 2006; Pandey et al., 2007).

The therapeutic utility of rapamycin in ASD was suggested in 2008 based on studies in *Tsc2*^{+/-} mice (Ehninger et al., 2008). The mTOR pathway is associated with TSC because TSC1 and TSC2 are upstream inhibitory regulators of mTOR activity (Han and Sahin, 2011). In this study, the learning and memory deficits, lethality, aberrant brain overgrowth, and altered synaptic plasticity of *Tsc2*^{+/-} mice were ameliorated by acute treatment with rapamycin (Table 4). The social dysfunction and behavioral inflexibility of Purkinje cell-specific *Tsc1* mutant mice were also improved by rapamycin (Tsai et al., 2012), further suggesting that rapamycin may be useful in reversing core symptoms of autism.

OXYTOCIN

Oxytocin is a nine amino acid neuropeptide hormone synthesized by magnocellular neurons in paraventricular and supraoptic nuclei of the hypothalamus and secreted from the posterior pituitary gland into the circulation (Figure 1). Oxytocin acts through oxytocin receptors (OXTRs), which are abundantly expressed in the amygdala, hippocampus, and hypothalamus (Gould and Zingg, 2003). Oxytocin is associated with various social behaviors including affiliation, maternity, aggression, and pair bonding (Lee et al., 2009; Caldwell, 2012; Feldman, 2012). Given the prominence of oxytocin in the regulation of social behavior, the association of oxytocin with autism pathogenesis has been extensively examined.

Several SNPs of OXTRs are associated with ASD (Wu et al., 2005; Jacob et al., 2007; Yrigollen et al., 2008; Liu et al., 2010). *Oxtr* knockout mice display autistic-like behaviors; they emit fewer USVs upon social isolation, show defects in social recognition and discrimination, and are less aggressive (Table 6) (Takayanagi et al., 2005; Crawley et al., 2007). Supporting the pharmacotherapeutic potential of oxytocin, nasal administration of oxytocin improves social interactions and communications (Andari et al., 2010; Kosaka et al., 2012), reduces repetitive behaviors (Hollander et al., 2003), and enhances social cognition (Hollander et al., 2007) in autism-affected individuals.

PERSPECTIVES

HOMEOSTATIC MECHANISMS UNDERLYING ASD

Tuberous sclerosis and fragile X syndrome are disorders with common symptoms including intellectual disabilities, seizures, and autism. While their genetic determinants are different (*TSC1/TSC2* for tuberous sclerosis and *FMR1* for fragile X syndrome), their gene products both regulate protein synthesis in neurons (Bassell and Warren, 2008; Ehninger et al., 2009). Interestingly, animal models of tuberous sclerosis (*Tsc2*^{+/-} mice) and fragile X syndrome (*Fmr1*^{-/-} mice) display abnormal protein synthesis in opposite directions (Auerbach et al., 2011).

Tsc2^{+/-} mice exhibit diminished mGluR-dependent LTD and protein synthesis in the hippocampus, whereas *Fmr1*^{-/-} mice show excessive mGluR-dependent LTD and protein synthesis. Consistent with this, cognitive impairments of the two animal models are corrected by drugs that modulate mGluR5 in the opposite manner (CDPPB for *Tsc2*^{+/-} mice and MPEP for *Fmr1*^{-/-} mice). In addition, crossbreeding of these two mouse lines rescues behavioral impairments and synaptic dysfunctions. These results strongly suggest that mGluR5-mediated synaptic plasticity and protein synthesis in the normal range is important and that deviation in either direction from a normal range can cause brain dysfunctions that yield similar behavioral manifestations.

Another such example comes from two mouse models with different mutations in the same gene. *Shank2*^{-/-} mouse lines lacking exons 6 and 7 (Won et al., 2012) or exon 7 only (Schmeisser et al., 2012), both of which mimic mutations found in humans (Berkel et al., 2010), display similar autistic-like behaviors, but NMDAR function in their brains shows opposite changes: NMDAR hypofunction with exons 6 and 7 deletion and NMDAR hyperfunction with exon 7 deletion. Although further details remain to be explored, this is another example

suggesting that NMDAR function in a normal range is important, and that deviations in either directions can lead to similar behavioral abnormalities. Therefore, individuals with mutations in the same gene may have to be carefully diagnosed, for example by high-throughput sequencing, in order to receive proper treatment.

CORE MECHANISMS UNDERLYING ASD

Given the diverse genetic variations underlying the development of ASD, one obvious challenge in understanding how ASD develops is the wide range of mechanisms associated with it. This diversity poses a serious additional problem in treating ASD: a single medication is likely to cover only a small fraction of individuals with ASD, or a limited spectrum of ASD symptoms.

A related well-known example is the selective effect of risperidone. Risperidone, a dopamine antagonist, is an antipsychotic mainly used to treat schizophrenia and bipolar disorder, and it is currently one of the few FDA-approved medications for autism. The drug mainly ameliorates irritability, hyperactivity, and repetitive and restricted behaviors, but is largely ineffective against social withdrawal and language deficits of autistic individuals (McPheeters et al., 2011). Similarly, risperidone rescues repetitive grooming and hyperactivity, but not social deficits, in *Cntnap2*^{-/-} mice (Penagarikano et al., 2011). Another example is the demonstration that CDPPB rescues only social interaction in *Shank2*-deficient mice but fails to rescue impaired pup retrieval, repetitive jumping, hyperactivity, and anxiety-like behavior (Won et al., 2012). The fact that some medications reverse only selective symptoms/phenotypes of ASD, however, may provide an opportunity to further explore detailed mechanisms underlying particular aspects of ASD etiology. This would, in principle, allow us to dissect and study synaptic or circuit mechanisms that are specifically associated with certain aspects of ASD, such as impaired social interaction, impaired social communication, repetitive behavior, restricted interests, intellectual disability, anxiety, and hyperactivity.

A possible solution to the apparent diversity of ASD-related mechanisms is to identify “core” mechanisms that cover a large fraction of genetic variations, or a broader spectrum of ASD symptoms. The concept of core mechanisms is based on the assumption that a fraction of ASD-related proteins may act together and converge on a common pathway. A possible core mechanism could be excitatory synaptic transmission. Excitatory synaptic development can be regulated by a number of factors including synaptic adhesion molecules, synaptic scaffolding proteins, and actin-regulatory proteins. In addition,

excitatory synaptic transmission, which is mainly mediated by AMPAR receptors, can be determined by the regulators of the synaptic trafficking and stabilization of AMPA receptors, and regulated by the signaling pathways in the downstream of NMDA receptors, mGluRs, and monoamine receptors. Another core mechanism could be the E-I balance, which is determined by the relative amounts of excitatory and inhibitory synaptic transmissions, and, together with the excitability of postsynaptic neurons, determines firing patterns of postsynaptic neurons and, subsequently, network activities across the brain. Establishing these core mechanisms, if any, would require rigorous and time-consuming verifications using a range of approaches, including mouse genetics, electrophysiology, and behavior.

INTEGRATING THREE ASPECTS OF ASD RESEARCH: HUMAN GENETICS, MOUSE MODELS, AND POTENTIAL TREATMENTS

An important starting point for ASD research using mouse models would be to select best possible genetic variations that can provide us decent insights into the underlying mechanisms and potential treatments. Luckily, a large number of ASD-related papers are being published each year (i.e., ~2500 papers in 2012 when “autism” was used as a search key word in PubMed). These publications, which use diverse genetic and genomic approaches and often large size samples, have identified overlapping genes and mutations, which are likely to have greater influences on the development of ASD. Characterization of transgenic mouse lines that carry these frequent genetic variations would help us efficiently obtain ASD mechanisms with a greater impact.

The synaptic and circuit mechanisms derived from ASD mouse model researches would provide clues to the ways to rescue synaptic/circuit phenotypes and ASD-like behaviors in mice. Given that there is no FDA-approved treatment for social deficits in ASD as of now, these rescue results will only be useful in supporting that the candidate mechanisms are indeed causing the ASD-like phenotypes in mice. Importantly, however, some of these mechanism-based rescues may serve as the basis for clinical trials. Eventually, some of the clinically verified medications may return to basic ASD research and be used to identify additional ASD mouse models with similar or novel underlying mechanisms, which will help us understand a bigger picture, where many synaptic and circuit mechanisms act together and converge into more comprehensive mechanisms.

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