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Bridging the Gap between Genes and Behavior: Brain-Derived Neurotrophic Factor and the mTOR Pathway in Idiopathic Autism

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Abstract

Although autism is highly genetic, "idiopathic" cases, for which there is no known genetic basis, may be due to epigenetic or environmental factors. Indeed, recent efforts have been highly successful in identifying hundreds of genes, as well as interacting epigenetic and environmental factors that contribute to autism susceptibility, corroborating the importance of gene x environment interactions in the etiology of autism. Nevertheless, a more thorough understanding of the proteins and pathways that lead from genes to behavior is desperately needed.

Genetic studies have implicated molecules involved in synapse development and plasticity in autism pathogenesis. Among these are brain-derived neurotrophic factor (BDNF), its receptor, tropomyosin-related kinase B (TrkB), and their signaling pathways including mammalian target of rapamycin (mTOR), which is increased in most forms of syndromic autism. Notably, abnormalities in these molecules have also been found in idiopathic autism. Postmortem brain tissue of subjects with idiopathic autism exhibits imbalances in BDNF isoforms, reduced TrkB and downstream effectors PI3 kinase (PI3K), mTOR, Epidermal growth factor receptor pathway substrate 8 (Eps8) and the excitatory synaptic marker postsynaptic density protein 95 kDa (PSD-95). Furthermore, similar TrkB pathway deficits including reduced TrkB/mTOR signaling and PSD-95, along with autistic-like behavior, have been found in valproic acid-exposed rodents, a model of environmental/epigenetic causes of autism. Our studies in both human idiopathic autism and the valproic acid-induced rodent model suggest that decreased signaling through the mTOR pathway can be as damaging as its over-activation.

Autism

Autism is a lifelong neurodevelopmental disorder characterized by disturbances in social interactions and communication and stereotyped, repetitive patterns of interests, activities and behaviors [1,2]. It is one of a heterogeneous group of disorders called Autism Spectrum Disorders (ASD) that share these characteristics but differ in course, symptom pattern or level of functioning. ASD is perhaps the most common and handicapping neurological disorder of childhood in terms of prevalence, morbidity, outcome and cost to society. ASD represents a significant public health problem and poses a huge burden for education and social service systems. Recent estimates of the prevalence of ASD in the US and Canada (CDC, NEDSAC) were 1 in 68 [3,4]. There is currently no diagnostic test or cure available for autism, and its etiology is unknown.

Epidemiological and twin studies point to a major role for genetic factors in ASD [5,6], with a complex pattern of transmission thought to be the result of perhaps as many as 1000 interacting genes [7-9]. Hundreds of rare genetic events that carry increased risk for ASD, many of them arising *de novo* [10-14], have been identified [15-21]. However, genetic changes account for only half of all autistic cases; environmental influences are responsible for the remaining half [22]. Cases of autism without known genetic abnormality are termed "idiopathic". Environmental factors causing idiopathic autism include *in utero* exposure to drugs such as valproic acid, environmental toxins such as pesticides, infection, paternal age, or other insults [23-29]. These environmental insults are thought to confer autism susceptibility by inducing epigenetic changes [30-36]. Involvement of epigenetic mechanisms in the etiology of idiopathic autism is supported by autistic behavior arising from epigenetic mutations (Fragile X syndrome) or disruption of key epigenetic regulatory factors (Rett syndrome) [37-39]. Further support for this hypothesis comes from recent exome sequencing studies showing that rare sequence variations in autism occur in genes coding for transcriptional and chromatin-remodeling proteins [7]. Together, these findings suggest that epigenetic dysregulation of gene expression might provide a link between gene and environment in autism pathogenesis.

The Synapse

Rare mutations and copy number variations in genes coding for synaptic proteins [40-45] suggest that alterations at synapses contribute to the behavioral and cognitive deficits of autistic subjects. Indeed, autism-linked mutations have been identified in genes involved in neurogenesis, neurite outgrowth and guidance, excitation-inhibition balance, and spine protein synthesis regulation [46]. Also, consistent with this evidence and supporting the hypothesis that synaptic dysfunction may play a major role in the etiology of ASD, animal models carrying autism-linked mutations in synaptic adhesion and scaffolding proteins, such as neuroligins and shanks, exhibit autistic-like behaviors [18,47]. These findings have focused attention on aberrant connectivity as an underlying cause of both genetically-linked ASD and idiopathic autism.

BDNF Biological Activity

Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays a key role in neuronal development and differentiation, axonal and dendritic growth and connectivity, cell morphology, regulation of synaptogenesis and dendritic spine homeostasis, excitation/inhibition balance, and synaptic transmission and plasticity [48-56] via some of the pathways known to be affected in ASD [57,58]. It also modulates long-term potentiation and is involved in learning, memory and attention [49,59]. Because of its pivotal role in guiding synaptic development, plasticity and cortical organization [53], BDNF is an essential molecule in brain development and thus a prime candidate for involvement in ASD.

BDNF Isoforms

BDNF is synthesized as a 32 kDa precursor, proBDNF, that can be processed to the 14 kDa mature form [60] either intracellularly [61] or extracellularly [62,63]. ProBDNF and BDNF are secreted molecules; proBDNF is thought to be the major form released at the dendrites, whereas in the soma it is secreted as mature BDNF after being processed in the Golgi [64]. ProBDNF exhibits distinct and opposite functions compared to mature BDNF, reducing dendritic spines and inducing apoptosis and long-term depression in cultured neurons. Conversely, mature BDNF promotes spine formation, neuronal survival and long-term potentiation [63,65-67]. This suggests that the correct balance between proBDNF and mature BDNF is crucial for synaptic development and plasticity, and that an imbalance of proBDNF and mature BDNF may contribute to synaptic abnormalities. Through a different cleavage, proBDNF also produces another BDNF isoform of 28 kDa called truncated BDNF, which is not further processed into mature BDNF [68]. The biological activities and roles of truncated BDNF are unknown.

Receptors

ProBDNF and BDNF bind to two different types of receptors. The first is TrkB, a receptor tyrosine kinase primarily responsible for transducing the survival, differentiation, spine maturation, and activity-dependent synapse strengthening functions of BDNF. TrkB is densely expressed on cortical and hippocampal neurons [54,69] and is involved in formation of both glutamatergic and GABAergic synapses during development [70-72]. With maturation, TrkB becomes enriched at excitatory synapses [73]. BDNF and proBDNF also bind to the low-affinity pan-neurotrophin receptor $p75^{NTR}$, implicated in opposing functions to TrkB including apoptosis, neurite retraction, and LTD [74,75]. ProBDNF binds more strongly to $p75^{NTR}$, whereas BDNF binds more strongly to TrkB [62], providing a balance in the brain between synaptic strengthening (BDNF/TrkB) and synaptic weakening (proBDNF/$p75^{NTR}$). Thus, to maintain a balance between the relative levels of BDNF isoforms and their receptors is essential for normal synaptic function and plasticity and for cortical circuitry development. Indeed, multiple studies have shown that changes in levels of proBDNF, truncated BDNF and mature BDNF and their receptors are implicated in neuropsychiatric disorders marked by altered cortical maturation and synaptic plasticity including schizophrenia [76-80], major depression [81,82] and neurodegenerative diseases [83-87].

TrkB Signaling

TrkB is expressed in three splice variants [88]. Full-length receptors (TrkB-FL) contain an intracellular catalytic tyrosine kinase domain, are expressed almost exclusively by pyramidal neurons and interneurons and mediate classic neurotrophic signaling. Conversely, the two truncated TrkB isoforms, TrkB-T1 and TrkB-Shc, are located on both neurons and glia and are able to bind and sequester BDNF but, lacking kinase activity, cannot elicit the normal cellular response to BDNF [89]. They thus may act as negative regulators of BDNF signaling [90]. Neurotrophic effects of BDNF depend on the relative levels of TrkB isoforms [89,91,92].

BDNF binding to TrkB-FL leads to the activation of several intracellular pathways, including the phosphoinositide-3'-kinase (PI3K) pathway and the mitogen-activated protein kinase (ERK) pathway [74,93], which play key roles in the developing and adult brain. Pathways downstream of PI3K that play a pivotal role in synapse formation and function include the Epidermal growth factor receptor pathway substrate 8 (Eps8)-Rac pathway modulating Rac-dependent actin cytoskeletal remodeling at synapses [94,95] and the Akt-mammalian target of rapamycin (mTOR) pathway controlling spine protein synthesis [96] (Figure 1).

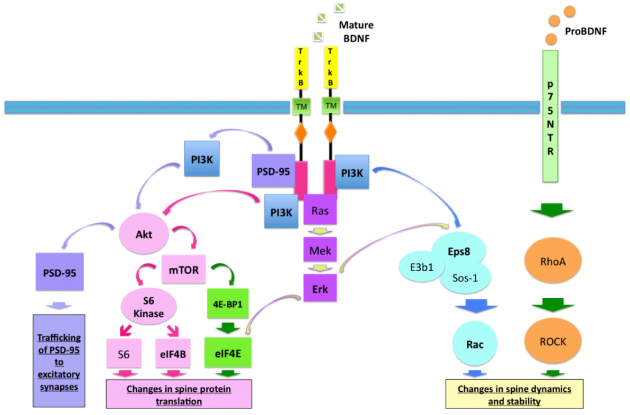

Figure 1. BDNF/TrkB/PI3K-activated intracellular signaling cascades involved in spine protein synthesis and actin remodeling at synapses. These include the Akt-mTOR pathway which regulates spine protein synthesis via two downstream signaling cascades, 4E-BP1/eIF4E and S6 kinase/S6, and the Eps8-Rac pathway modulating Rac-dependent actin cytoskeletal reorganization. Additionally, Erk signaling contributes to BDNF-dependent regulation of translation and cytoskeletal remodeling through phosphorylation of eIF4E and Eps8, respectively, and TrkB signaling through PI3K recruits PSD-95 to spines. Lastly, proBDNF/$p75^{NTR}$ opposes Eps8/Rac and destabilizes dendritic spines.

Specifically, mTOR influences protein translation at spines via two downstream pathways which are responsible for promoting translation of different pools of mRNAs [97]. One pathway involves S6 kinase and the eukaryotic initiation factor 4B (eIF4B), while the other comprises the eukaryotic initiation factor 4E (eIF4E) and its binding protein 1 (4E-BP1) [97-99]. A third pathway, the Erk signaling cascade, also contributes to regulation of local translation by BDNF through eIF4E phosphorylation [100,101]. Lastly, proBDNF/$p75^{NTR}$

signals through several pathways, including RhoA [74,75], which opposes the Eps8-Rac pathway to promote spine or neurite retraction.

BDNF and TrkB in ASD

The molecular underpinnings of ASD remain unknown. Genetic, anatomical and functional imaging studies suggest that defects in synaptic development and plasticity, which impair establishment and maintenance of functional neuronal networks, underlie the clinical symptoms of autism. BDNF, TrkB and their signaling pathways, including Akt-mTOR and Eps8/Rac, play a key role in the development of the cortex and in synaptic function and plasticity [74,93]. It follows that altered BDNF/TrkB signaling through these pathways might be an important substrate of autism pathogenesis. Multiple studies using ELISAs have reported elevated BDNF-immunoreactive protein in cord blood [102], serum [103,104] platelet-rich plasma [105] and brain [106,107] from ASD *vs.* control subjects. Specific BDNF SNP haplotypes are associated with autism [108], as are multiple SNPs and haplotypes of the TrkB gene, NTRK2 [105]. Furthermore, potential links between alterations in BDNF/TrkB-mediated signaling pathways and ASD are supported by reports of decreased phosphorylated and total Akt protein in the frontal cortex of autistic patients [109]. Also, mutations in Akt-mTOR cascade components, including hamartin (TSC1), tuberin (TSC2), phosphatase and tensin homolog on chromosome ten (PTEN) and methyl-CpG-binding protein 2 (MeCP2), cause monogenic disorders with high rates of autism [40,110-112]. In addition, single nucleotide insertions in the promoter of mTOR downstream effector eIF4E have been found in autistic patients [113], and autism-like phenotypes have been observed in eIF4EBP2 knockout and eIF4E-overexpressing mice [114]. Collectively, these findings strengthen the hypothesis that defective BDNF/TrkB-mediated pathways contribute to autism pathology, likely by disrupting mTOR-dependent protein synthesis.

De-Regulated mTOR, Dendritic Spines and Synaptic Transmission

mTOR is a key "hub" in the control of spine protein synthesis and neuronal survival, and either too much or too little signaling through this pathway can result in autistic behavior. For example, mutations in TSC1/2 and PTEN, which activate the PI3K-Akt-mTOR pathway, lead to tuberous sclerosis complex and macrocephaly, respectively, disorders exhibiting a high prevalence of autism [40,113]. Conversely, mutations in MeCP2, a transcriptional regulator that acts through epigenetic changes in chromatin structure, reduce BDNF expression and mTOR pathway signaling and cause Rett syndrome, which like tuberous sclerosis complex and macrocephaly, is another monogenic disorder associated with high rates of autism [115,116]. This suggests that either hypo- or hyper-activation of mTOR, leading to deficient or excessive protein synthesis at synapses, may be equally disruptive; optimal synaptic function appears to occur within a narrow range [110,117].

mTOR regulates dendrite growth and dendritic spine morphogenesis [96,118,119]. Both up- and down-regulation of the mTOR pathway result in abnormal spine morphology and density as seen in tuberous sclerosis complex (increased mTOR), fragile X (increased mTOR) and Rett (decreased mTOR) syndrome animal models and patients [112]. Specifically, both tuberous sclerosis complex and Rett syndrome are characterized by a decreased number of spines, with the spines that are present having elongated necks [119-122]. However, spine heads are enlarged in tuberous sclerosis complex [119], while they are reduced in Rett syndrome [121]. Lastly, patients and rodent models of fragile X syndrome have an increased density of long and thin (immature) spines [123-127]. Alterations in dendritic spines, which are the principle site of excitatory synapses [128-131], are likely to impair establishment and remodelling of cortical networks that subserve higher cognitive functions and behavior. Hence, by perturbing dendritic spines (excitatory synapses), a hypo- or hyper-activated mTOR pathway impairs connectivity in neuronal circuits and thus contributes to autism etiology. Further support for this hypothesis comes from the evidence that reduced TrkB-mTOR signaling is associated with a significant decrease in protein expression of the excitatory synaptic marker PSD-95 in patients with idiopathic autism [132], suggesting fewer excitatory synapses. Lastly, knockout of the TrkB-activated actin-capping molecule Eps8 results in widespread abnormalities in spine morphology and function, decreased LTP and autism-like symptoms [115]. Taken together, these data support the model that defective TrkB-mTOR signaling disrupts spine density, morphology and function, hence playing a key role in aberrant connectivity during development and thereby in the etiology of autistic traits.

It is has been demonstrated recently that mTOR not only plays a role in regulating development and plasticity of excitatory synapses, but also in controlling GABAergic transmission [133]. It is thus possible that de-regulated mTOR might adversely affect GABAergic synaptic activity. Notably, abnormal GABAergic transmission has been observed in Fmr1 knockout (KO) mice [134-136] and MeCP2 null mice [137,138]. In particular, Fmr1-KO mice have enhanced GABA-mediated synaptic transmission [134], while GABAergic synaptic transmission is greatly reduced in MeCP2 deficient mice [137,138]. This suggests that either too much or too little mTOR perturbs neuronal networks and contributes to autistic behavior by altering both glutamatergic and GABAergic synapses.

Interestingly, autistic-like behaviors in mouse models can be reversed in the adult by administration of mTOR inhibitors [139,140] or activators [141]. Tsc2+/- mice have increased Akt-mTOR signaling and impaired social behavior, both of which were rescued by treatment with the mTOR inhibitor rapamycin [139]. MeCP2 (Rett) mice have reduced BDNF, which has been linked to abnormal excitability, as well as reduced Akt-mTOR signaling and protein synthesis, which are associated with disease progression [142,143]. Increasing BDNF expression in these mice rescues TrkB/Akt signaling and breathing dysfunction [143]. Also, treatment with insulin-like growth factor 1 (IGF-1) which, like BDNF, activates the mTOR pathway [144], rescues synaptic deficits and social and anxiety behavior in MeCP2 mice and in human Rett syndrome [141,145]. Reversal of autistic behavior in these genetic models of ASD, particularly in Rett syndrome, which arises from a mutation in an epigenetic regulatory gene, supports the exciting possibility that autistic behavior can also be reversed in idiopathic autism.

Molecular Studies in Human Postmortem Brain

Distinct areas of the brain are associated with the behavioral deficits of ASD patients [146]. For example, disruptions of the fusiform gyrus area of cortex are associated with poor social skills and difficulty with face perception [147-152]. Therefore, we examined fusiform gyrus using a molecular approach [106]. Postmortem brain samples from subjects with autism and matched controls were provided to us by the Autism Speaks' Autism Tissue Program (ATP, Princeton, NJ), the

Harvard Brain Tissue Resource Center (Belmont, MA) and the NICHD Brain and Tissue Bank (University of Maryland, Baltimore). To reduce heterogeneity, we selected subjects with idiopathic autism and excluded autism spectrum and related genetic disorders such as Asperger's, Rett syndrome, and PDD-NOS.

BDNF Isoform Imbalance in Idiopathic Autism

In agreement with previous studies, using ELISAs, we found elevated BDNF-immunoreactivity in postmortem fusiform gyrus of subjects with autism compared to controls [106]. These data confirm a neurochemical abnormality in a brain region implicated in social interaction deficits in ASD. However, ELISAs cannot distinguish between the three BDNF protein isoforms. Thus, we quantified BDNF isoforms in autistic and control fusiform gyrus using Western blotting. We found elevated proBDNF and decreased truncated BDNF protein levels but no difference in BDNF mRNA levels [106] in fusiform gyrus of autism subjects compared to controls.

Decreased Catalytic TrkB and TrkB Signaling in Idiopathic Autism

We also found decreased full-length TrkB (TrkB-FL) isoform levels in autism postmortem fusiform gyrus [132]. This decrease in TrkB-FL protein levels is not due to changes in relative amounts of neurons *vs.* glia. Indeed, we observed no difference in the protein levels of neuronal (βIII-Tubulin) or glial (GFAP) markers between autism and control samples [132]. Furthermore, we demonstrated reduced BDNF/TrkB downstream effectors PI3K, Akt, mTOR, S6 kinase (p70 S6K) and eIF4B protein expression [132], suggesting decreased translation of mRNAs mainly encoding components of the translational machinery (Figure 2).

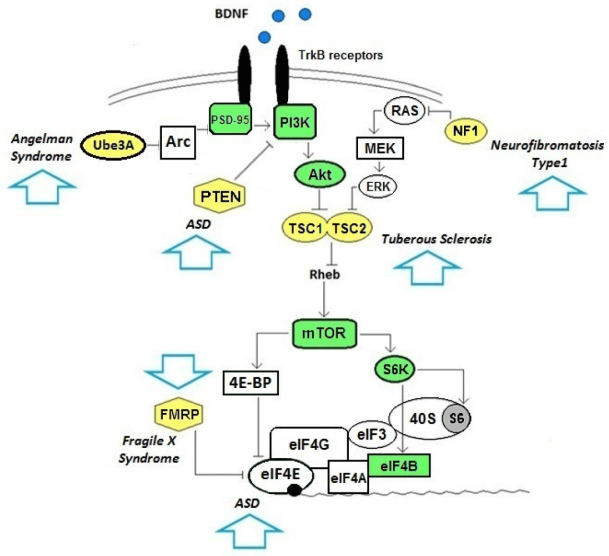

Figure 2. Schematic diagram of BDNF/TrkB and downstream pathways through Ras-Mek-Erk and PI3K-Akt-mTOR. Yellow indicates proteins implicated in single-gene disorders associated with high rates of autism. Green indicates proteins implicated in our study of idiopathic autism. White indicates proteins that do not exhibit differences between idiopathic autism and control (Erk, 4E-BP, eIF4E) or that have not yet been tested.

Signaling is reduced through this pathway: reduced phosphorylation of mTOR is evident in fusiform gyrus of autism *vs.* control subjects [132]. No significant changes in 4E-BP1 or eIF4E protein levels were found in the same cohort [132], nor was there a difference between groups in Erk protein expression [115], demonstrating the specificity of the pathway deficit. These findings are consistent with the model that the key role BDNF plays in development of the cortex is in part mediated by activation of the PI3K-Akt-mTOR signaling pathway, which affects dendritic arborization and local protein synthesis in dendrites [96]. Additionally, these results support the idea that hypo-activation of the mTOR pathway may, like hyper-activation, contribute to autistic behavior [110,117].

A separate pathway downstream of PI3K activates Eps8, an actin-capping molecule that controls spine stability and filopodial motility in response to BDNF [153]. The Eps8 pathway signals through Rac, which stabilizes dendritic spines, and is opposed by Rho, which destabilizes spines [154]. We found significantly decreased Eps8 in autism *vs.* control fusiform gyrus [115], suggesting an imbalance in the Rac/Rho pathway influencing spine density and maturation. Together with decreased Eps8/Rac signaling, increased proBDNF in autism, acting through $p75^{NTR}$ to activate Rho, may unbalance the Rac/Rho pathway. This may destabilize spines and reduce neuritogenesis (Figure 1). The importance of this pathway for autism is corroborated by the fact that Eps8 knockout mice exhibit autistic-like behavior and aberrant LTP and spine morphology [115].

Notably, disruptions of BDNF/TrkB signaling cascades are associated with significant reductions in the excitatory postsynaptic marker PSD-95 in autism *vs.* control fusiform gyrus [132]. PSD-95 is a

scaffolding protein essential for synaptic organization and function. It forms a complex with TrkB, thereby promoting signaling through PI3K-Akt, which in turn induces synaptic localization of PSD-95, crucial for both synapse formation and synaptic plasticity [93,155]. Taken together, these findings suggest that imbalances in BDNF/TrkB signaling may ultimately affect excitatory synapses and consequently the development and maintenance of cortical circuits, thus contributing to autism's cognitive and behavioral deficits.

Consistent with this hypothesis, our studies showed that abnormalities in BDNF isoforms [106], TrkB and their downstream signaling pathways [132] are widespread in the brains of subjects with idiopathic autism (excluding subjects with other disorders on the spectrum or with known genetic causes of autism). In idiopathic autism, there is decreased TrkB signaling through the PI3K/Akt/mTOR pathway [132] and through the Eps8/Rac pathway [115], whereas proBDNF is increased [106]. This is in contrast to neurodevelopmental disorders with high rates of autism such as tuberous sclerosis, neurofibromatosis type I and Fragile X syndrome. The mutated genes in these disorders normally apply "brakes" to the mTOR pathway. Their mutation causes increased mTOR pathway signaling, the opposite of the decrease we see when there are deficits in the "accelerator", TrkB (Figure 2). Thus, an imbalance in either direction in this pathway appears to result in autistic behavior.

Although many of the genes in these and related pathways have been implicated in recent genetic studies of ASD, their protein products had not been examined in autistic brain. The importance of fully documenting changes in these signaling cascades in postmortem tissue cannot be understated. It is difficult, if not impossible, to move to translational work (targeting specific molecules for therapy) without full knowledge of the underlying molecular dysfunction in the human brain, which, as demonstrated here, may differ between genetic and epigenetic syndromes. To further investigate the relationship of TrkB signaling deficits to autistic behavior, we have now moved to an animal model that mirrors the molecular changes described above. We have chosen the valproic acid (VPA)-exposed rodent because of its validity as a model for the pathways and behavior under study, and as a model for possible epigenetic origins of idiopathic autism.

Maternal Challenge with VPA as a Model of Idiopathic Autism

Valproic acid (VPA) is a known risk factor for autism. This fatty acid is used widely as an antiepileptic drug [156] and for the treatment of mood disorders [157,158]. VPA regulates gene expression through (epigenetic) chromatin remodeling by inhibition of histone deacetylase activity [159]. Maternal exposure to VPA at the time of neural tube closure increases the risk of autism in humans [160-163] and causes autistic-like symptoms in rodents [164,165]. A single exposure to VPA *in utero* causes impaired social interactions, stereotypical hyperactivity and sensory/communication deficits in rodents' offspring [164-167]. Rodents prenatally exposed to VPA also show anatomical and molecular alterations similar to human autism including decreased cerebellar volume and Purkinje cell number [163,168,169], disrupted spine density and morphology [170-172], decreased expression of the autism-associated postsynaptic adhesion molecule Neuroligin 3 [173], and increased NR2A and NR2B NMDA receptor subunits [171]. Furthermore, rats prenatally exposed to VPA prior to formation of the neocortex have perturbed cortical connectivity along with abnormal synapse formation and pruning [174,175]. Additionally, in line with the evidence that postulates a disruption of the excitatory/inhibitory circuit balance in human autism [176], VPA-exposed mice exhibit a decrease in parvalbumin (PV)-positive interneurons in parietal and occipital cortices [177]. Lastly, like humans, VPA-treated rats respond successfully to early environmental enrichment [178]. Taken together, these findings support face, construct and predictive validity of the VPA-induced rodent model. Although much of today's ASD research uses transgenic mouse models carrying mutations in single genes known to cause autism or related developmental disorders, a model of epigenetic changes such as the VPA-exposed rodent might better represent the many idiopathic autism cases having no known genetic basis.

We have determined that molecular abnormalities similar to those we demonstrated in the brain of subjects with idiopathic autism are detectable in postnatal day (PND) 35-38 rats whose dams were injected with VPA on embryonic day E12.5 [132]. VPA-exposed offspring have Akt-mTOR signaling deficits consistent with human autistic brain tissue [132]. They also exhibit ASD-like behaviors including decreased social play behavior [179-180]. These data suggest that VPA-treated rodents are a suitable animal model for further studies of autism and can be used to determine the contribution of BDNF/TrkB/mTOR signaling abnormalities to the behavioral symptoms and synaptic deficits of autism. Furthermore, the VPA rodent model appears to be a valuable tool to investigate whether pharmacological intervention of the TrkB-mTOR pathway can ameliorate autistic behavior.

Conclusions

Recent years have seen major advances in both the genetics and the behavioral aspects of autism. Yet there is still relatively little research on the molecular mechanisms that link genes to behavior. Our analysis of protein expression and post-translational regulation in postmortem human brain tissue has led to some unique insights. We demonstrated that, unlike most single-gene disorders with high rates of autism, postmortem brain tissue from subjects with idiopathic autism exhibits decreased mTOR pathway signaling. This supports a growing realization that either too much or too little signaling can lead to similar synaptic deficits. In addition, we corroborated the validity of the VPA-exposed rodent as an experimental model of idiopathic autism, since it reflects molecular changes evident in idiopathic cases of autism and is epigenetic in origin as opposed to genetic models. Understanding the molecular and synaptic dysfunction associated with autism by studying both human and rodent brain may lead to a better understanding of the heterogeneity of ASD and to the identification of new therapeutic targets.

References

1. DSM-5- Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition, Washington DC, American Psychiatric Association, 2013.
2. Lahey BB, Pelham WE, Chronis A, Massetti G, Kipp H, et al. (2006) Predictive validity of ICD-10 hyperkinetic disorder relative to DSM-IV attention-deficit/hyperactivity disorder among younger children. J Child Psychol Psychiatry 47: 472-479.
3. CDC MMWR: Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010. Surveillance Summaries March 28, 2014.
4. Findings from the National Epidemiologic Database for the Study of Autism in Canada (NEDSAC): Changes in the Prevalence of Autism Spectrum Disorders in Newfoundland and Labrador, Prince Edward Island, and Southeastern Ontario. March 2012.

5. Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, et al. (1995) Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med 25: 63-77.
6. Fombonne E (1998) Epidemiological surveys of autism. F. Volkmar (ed.), Autism and Pervasive Developmental Disorders, Cambridge University Press.
7. De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, et al. (2014) Synaptic, transcriptional and chromatin genes disrupted in autism. Nature 515: 209-215.
8. Gaugler T, Klei L, Sanders SJ, Bodea CA, Goldberg AP, et al. (2014) Most genetic risk for autism resides with common variation. Nat Genet 46: 881-885.
9. Iossifov I, O'Roak BJ, Sanders SJ, Ronemus M, Krumm N, et al. (2014) The contribution of de novo coding mutations to autism spectrum disorder. Nature 515: 216-221.
10. Iossifov I, Ronemus M, Levy D, Wang Z, Hakker I, et al. (2012) De novo gene disruptions in children on the autistic spectrum. Neuron 74: 285-299.
11. Neale BM1, Kou Y, Liu L, Ma'ayan A, Samocha KE, et al. (2012) Patterns and rates of exonic de novo mutations in autism spectrum disorders. Nature 485: 242-245.
12. O'Roak BJ, Vives L, Girirajan S, Karakoc E, Krumm N, et al. (2012) Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. Nature 485: 246-250.
13. Ronemus M1, Iossifov I, Levy D1, Wigler M (2014) The role of de novo mutations in the genetics of autism spectrum disorders. Nat Rev Genet 15: 133-141.
14. Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, et al. (2012) De novo mutations revealed by whole-exome sequencing are strongly associated with autism. Nature 485: 237-241.
15. Betancur C (2011) Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting. Brain Res 1380: 42-77.
16. Chang J, Gilman SR, Chiang AH, Sanders SJ, Vitkup D (2015) Genotype to phenotype relationships in autism spectrum disorders. Nat Neurosci 18: 191-198.
17. Devlin B, Scherer SW (2012) Genetic architecture in autism spectrum disorder. Curr Opin Genet Dev 22: 229-237.
18. Huguet G, Ey E, Bourgeron T (2013) The genetic landscapes of autism spectrum disorders. Annu Rev Genomics Hum Genet 14: 191-213.
19. Liu X, Takumi T (2014) Genomic and genetic aspects of autism spectrum disorder. Biochem Biophys Res Commun 452: 244-253.
20. Pinto D, Delaby E, Merico D, Barbosa M, Merikangas A, et al. (2014) Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. Am J Hum Genet 94: 677-694.
21. Yuen R, Thiruvahindrapuram B, Merico D, Walker S, Tammimies K, et al. (2015) Whole-genome sequencing of quartet families with autism spectrum disorder. Nat Med 21: 185-191.
22. Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, et al. (2014) The familial risk of autism. JAMA 311: 1770-1777.
23. Berko ER, Suzuki M, Beren F, Lemetre C, Alaimo CM, et al. (2014) Mosaic epigenetic dysregulation of ectodermal cells in autism spectrum disorder. PLoS Genet 10: e1004402.
24. Moore SJ, Turnpenny P, Quinn A, Glover S, Lloyd DJ, et al. (2000) A clinical study of 57 children with fetal anticonvulsant syndromes. J Med Genet 37: 489-497.
25. Rasalam AD, Hailey H, Williams JH, Moore SJ, Turnpenny PD, et al. (2005) Characteristics of fetal anticonvulsant syndrome associated autistic disorder. Dev Med Child Neurol 47: 551-555.
26. St-Hilaire S, Ezike VO, Stryhn H, Thomas MA (2012) An ecological study on childhood autism. Int J Health Geogr 11: 44.
27. Tordjman S, Somogyi E, Coulon N, Kermarrec S, Cohen D, et al. (2014) Gene × Environment interactions in autism spectrum disorders: role of epigenetic mechanisms. Front Psychiatry 5: 53.
28. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R (2013) Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry 70: 71-77.
29. Williams G, King J, Cunningham M, Stephan M, Kerr B, et al. (2001) Fetal valproate syndrome and autism: additional evidence of an association. Dev Med Child Neurol 43: 202-206.
30. Bushnell PJ (2013) Special issue: Environmental influences and emerging mechanisms in the etiology of autism. Neurotoxicol Teratol 36: 1-2.
31. Chaste P, Leboyer M (2012) Autism risk factors: genes, environment, and gene-environment interactions. Dialogues Clin Neurosci 14: 281-292.
32. Flashner BM1, Russo ME, Boileau JE, Leong DW, Gallicano GI (2013) Epigenetic factors and autism spectrum disorders. Neuromolecular Med 15: 339-350.
33. LaSalle JM (2013) Epigenomic strategies at the interface of genetic and environmental risk factors for autism. J Hum Genet 58: 396-401.
34. Miyake K, Hirasawa T, Koide T, Kubota T (2012) Epigenetics in autism and other neurodevelopmental diseases. Adv Exp Med Biol 724: 91-98.
35. Siniscalco D, Cirillo A, Bradstreet JJ, Antonucci N (2013) Epigenetic findings in autism: new perspectives for therapy. Int J Environ Res Public Health 10: 4261-4273.
36. Wong CC, Meaburn EL, Ronald A, Price TS, Jeffries AR, et al. (2014) Methylomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioural traits. Mol Psychiatry 19: 495-503.
37. Chahrour M, Jung SY, Shaw C, Zhou X, Wong ST, et al. (2008) MeCP2, a key contributor to neurological disease, activates and represses transcription. Science 320: 1224-1229.
38. Katz DM (2014) Brain-derived neurotrophic factor and Rett syndrome. Handb Exp Pharmacol 220: 481-495.
39. Schanen NC (2006) Epigenetics of autism spectrum disorders. Hum Mol Genet 15 Spec No 2: R138-150.
40. Bourgeron T (2009) A synaptic trek to autism. Curr Opin Neurobiol 19: 231-234.
41. Lionel AC, Vaags AK, Sato D, Gazzellone MJ, Mitchell EB, et al. (2013) Rare exonic deletions implicate the synaptic organizer Gephyrin (GPHN) in risk for autism, schizophrenia and seizures. Hum Mol Genet 22: 2055-2066.
42. Parikshak NN, Luo R, Zhang A, Won H, Lowe JK, et al. (2013) Integrative functional genomic analyses implicate specific molecular pathways and circuits in autism. Cell 155: 1008-1021.
43. Pinto D, Pagnamenta AT, Klei L, Anney R, Merico D, et al. (2010) Functional impact of global rare copy number variation in autism spectrum disorders. Nature 466: 368-372.
44. Autism Genome Project Consortium, Szatmari P, Paterson AD, Zwaigenbaum L, Roberts W, et al. (2007) Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nat Genet 39: 319-328.
45. Toro R, Konyukh M, Delorme R, Leblond C, Chaste P, et al. (2010) Key role for gene dosage and synaptic homeostasis in autism spectrum disorders. Trends Genet 26: 363-372.
46. Hussman JP, Chung RH, Griswold AJ, Jaworski JM, Salyakina D, et al. (2011) A noise-reduction GWAS analysis implicates altered regulation of neurite outgrowth and guidance in autism. Mol Autism 2: 1.
47. Banerjee S, Riordan M1, Bhat MA (2014) Genetic aspects of autism spectrum disorders: insights from animal models. Front Cell Neurosci 8: 58.
48. Chapleau CA, Larimore JL, Theibert A, Pozzo-Miller L (2009) Modulation of dendritic spine development and plasticity by BDNF and vesicular trafficking: fundamental roles in neurodevelopmental disorders associated with mental retardation and autism. J Neurodev Disord 1: 185-196.
49. Fahnestock M (2011) BDNF: The link between beta-amyloid and memory loss. Future Neurology 6: 627-639.
50. Horch HW (2004) Local effects of BDNF on dendritic growth. Rev Neurosci 15: 117-129.

51. Huang EJ, Reichardt LF (2001) Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 24: 677-736.
52. Jeanneteau F, Deinhardt K, Miyoshi G, Bennett AM, Chao MV (2010) The MAP kinase phosphatase MKP-1 regulates BDNF-induced axon branching. Nat Neurosci 13: 1373-1379.
53. Leal, Comprido D, Duarte CB (2014) BDNF-induced local protein synthesis and synaptic plasticity. Neuropharmacology 76 Pt C: 639-656.
54. McAllister AK, Lo DC, Katz LC (1995) Neurotrophins regulate dendritic growth in developing visual cortex. Neuron 15: 791-803.
55. Pencea V, Bingaman KD, Wiegand SJ, Luskin MB (2001) Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum, septum, thalamus, and hypothalamus. J Neurosci 21: 6706-6717.
56. Rutherford LC, Nelson SB, Turrigiano GG (1998) BDNF has opposite effects on the quantal amplitude of pyramidal neuron and interneuron excitatory synapses. Neuron 21: 521-530.
57. Miyamoto Y, Yamauchi J, Tanoue A, Wu C, Mobley WC (2006) TrkB binds and tyrosine-phosphorylates Tiam1, leading to activation of Rac1 and induction of changes in cellular morphology. Proc Natl Acad Sci U S A 103: 10444-10449.
58. Yuan XB, Jin M, Xu X, Song YQ, Wu CP, et al. (2003) Signalling and crosstalk of Rho GTPases in mediating axon guidance. Nat Cell Biol 5: 38-45.
59. Tyler WJ, Alonso M, Bramham CR, Pozzo-Miller LD (2002) From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. Learn Mem 9: 224-237.
60. Seidah NG, Benjannet S, Pareek S, Chrétien M, Murphy RA (1996) Cellular processing of the neurotrophin precursors of NT3 and BDNF by the mammalian proprotein convertases. FEBS Lett 379: 247-250.
61. Mowla SJ, Farhadi HF, Pareek S, Atwal JK, Morris SJ, et al. (2001) Biosynthesis and post-translational processing of the precursor to brain-derived neurotrophic factor. J Biol Chem 276: 12660-12666.
62. Lee R, Kermani P, Teng KK, Hempstead BL (2001) Regulation of cell survival by secreted proneurotrophins. Science 294: 1945-1948.
63. Pang PT, Teng HK, Zaitsev E, Woo NT, Sakata K, et al. (2004) Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. Science 306: 487-491.
64. Barker PA (2009) Whither proBDNF? Nat Neurosci 12: 105-106.
65. Koshimizu H, Kiyosue K, Hara T, Hazama S, Suzuki S, et al. (2009) Multiple functions of precursor BDNF to CNS neurons: negative regulation of neurite growth, spine formation and cell survival. Mol Brain 2: 27.
66. Teng HK, Teng KK, Lee R, Wright S, Tevar S, et al. (2005) ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. J Neurosci 25: 5455-5463.
67. Woo NH, Teng HK, Siao CJ, Chiaruttini C, Pang PT, et al. (2005) Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. Nat Neurosci 8: 1069-1077.
68. Seidah NG, Mowla SJ, Hamelin J, Mamarbachi AM, Benjannet S, et al. (1999) Mammalian subtilisin/kexin isozyme SKI-1: a widely expressed proprotein convertase with a unique cleavage specificity and cellular localization. Proc Natl Acad Sci USA 96: 1321-1326.
69. McAllister AK (2002) Neurotrophins and cortical development. Results Probl Cell Differ 39: 89-112.
70. Seil FJ (1999) BDNF and NT-4, but not NT-3, promote development of inhibitory synapses in the absence of neuronal activity. Brain Res 818: 561-564.
71. Seil FJ, Drake-Baumann R (2000) TrkB receptor ligands promote activity-dependent inhibitory synaptogenesis. J Neurosci 20: 5367-5373.
72. Spenger C, Hyman C, Studer L, Egli M, Evtouchenko L, et al. (1995) Effects of BDNF on dopaminergic, serotonergic, and GABAergic neurons in cultures of human fetal ventral mesencephalon. Exp Neurol 133: 50-63.
73. Gomes RA, Hampton C, El-Sabeawy F, Sabo SL, McAllister AK (2006) The dynamic distribution of TrkB receptors before, during, and after synapse formation between cortical neurons. J Neurosci 26: 11487-11500.
74. Kaplan DR, Miller FD (2000) Neurotrophin signal transduction in the nervous system. Curr Opin Neurobiol 10: 381-391.
75. Roux PP, Barker PA (2002) Neurotrophin signaling through the p75 neurotrophin receptor. Prog Neurobiol 67: 203-233.
76. Carlino D, Leone E, Di Cola F, Baj G, Marin R, et al. (2011) Low serum truncated-BDNF isoform correlates with higher cognitive impairment in schizophrenia. J Psychiatr Res 45: 273-279.
77. Hung YY, Huang TL (2013) Lower serum tropomyosin receptor kinase B levels in patients with schizophrenia. Biomed J 36: 132-136.
78. Weickert CS, Ligons DL, Romanczyk T, Ungaro G, Hyde TM, et al. (2005) Reductions in neurotrophin receptor mRNAs in the prefrontal cortex of patients with schizophrenia. Mol Psychiatry 10: 637-650.
79. Wong J, Hyde TM, Cassano HL, Deep-Soboslay A, Kleinman JE, et al. (2010) Promoter specific alterations of brain-derived neurotrophic factor mRNA in schizophrenia. Neuroscience 169: 1071-1084.
80. Wong J, Rothmond DA, Webster MJ, Weickert CS (2013) Increases in two truncated TrkB isoforms in the prefrontal cortex of people with schizophrenia. Schizophr Bull 39: 130-140.
81. Hung YY, Lin CJ, Huang TL (2010) Higher serum tropomyosin-related kinase B protein level in major depression. Prog Neuropsychopharmacol Biol Psychiatry 34: 610-612.
82. Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, et al. (2002) Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res 109: 143-148.
83. Holsinger RM, Schnarr J, Henry P, Castelo VT, Fahnestock M (2000) Quantitation of BDNF mRNA in human parietal cortex by competitive reverse transcription-polymerase chain reaction: decreased levels in Alzheimer's disease. Brain Res Mol Brain Res 76: 347-354.
84. Michalski B, Fahnestock M (2003) Pro-brain-derived neurotrophic factor is decreased in parietal cortex in Alzheimer's disease. Brain Res Mol Brain Res 111: 148-154.
85. Murer MG, Yan Q, Raisman-Vozari R (2001) Brain-derived neurotrophic factor in the control human brain, and in Alzheimer's disease and Parkinson's disease. Prog Neurobiol 63: 71-124.
86. Peng , Wuu J, Mufson EJ, Fahnestock M (2005) Precursor form of brain-derived neurotrophic factor and mature brain-derived neurotrophic factor are decreased in the pre-clinical stages of Alzheimer's disease. J Neurochem 93: 1412-1421.
87. Zuccato C, Marullo M, Conforti P, MacDonald ME, Tartari M, et al. (2008) Systematic assessment of BDNF and its receptor levels in human cortices affected by Huntington's disease. Brain Pathol 18: 225-238.
88. Barbacid M (1995) Structural and functional properties of the TRK family of neurotrophin receptors. Ann N Y Acad Sci 766: 442-458.
89. Eide FF, Vining ER, Eide BL, Zang K, Wang XY, et al. (1996) Naturally occurring truncated trkB receptors have dominant inhibitory effects on brain-derived neurotrophic factor signaling. J Neurosci 16: 3123-3129.
90. Fenner BM (2012) Truncated TrkB: beyond a dominant negative receptor. Cytokine Growth Factor Rev 23: 15-24.
91. Armanini MP, McMahon SB, Sutherland J, Shelton DL, Phillips HS (1995) Truncated and catalytic isoforms of trkB are co-expressed in neurons of rat and mouse CNS. Eur J Neurosci 7: 1403-1409.
92. Luberg K, Wong J, Weickert CS, Timmusk T (2010) Human TrkB gene: novel alternative transcripts, protein isoforms and expression pattern in the prefrontal cerebral cortex during postnatal development. J Neurochem 113: 952-964.
93. Yoshii A, Constantine-Paton M (2010) Postsynaptic BDNF-TrkB signaling in synapse maturation, plasticity, and disease. Dev Neurobiol 70: 304-322.
94. Innocenti M, Frittoli E, Ponzanelli I, Falck JR, Brachmann SM, et al. (2003) Phosphoinositide 3-kinase activates Rac by entering in a complex with Eps8, Abi1, and Sos-1. J Cell Biol 160: 17-23.

95. Offenhäuser N, Borgonovo A, Disanza A, Romano P, Ponzanelli I, et al. (2004) The eps8 family of proteins links growth factor stimulation to actin reorganization generating functional redundancy in the Ras/Rac pathway. Mol Biol Cell 15: 91-98.
96. Jaworski J, Spangler S, Seeburg DP, Hoogenraad CC, Sheng M (2005) Control of dendritic arborization by the phosphoinositide-3'-kinase-Akt-mammalian target of rapamycin pathway. J Neurosci 25: 11300-11312.
97. Santos AR, Comprido D, Duarte CB (2010) Regulation of local translation at the synapse by BDNF. Prog Neurobiol 92: 505-516.
98. Hay N, Sonenberg N (2004) Upstream and downstream of mTOR. Genes Dev 18: 1926-1945.
99. Santini E, Klann E (2011) Dysregulated mTORC1-Dependent Translational Control: From Brain Disorders to Psychoactive Drugs. Front Behav Neurosci 5: 76.
100. Bramham CR, Wells DG (2007) Dendritic mRNA: transport, translation and function. Nat Rev Neurosci 8: 776-789.
101. Takei N, Kawamura M, Hara K, Yonezawa K, Nawa H (2001) Brain-derived neurotrophic factor enhances neuronal translation by activating multiple initiation processes: comparison with the effects of insulin. J Biol Chem 276: 42818-42825.
102. Nelson KB, Grether JK, Croen LA, Dambrosia JM, Dickens BF, et al. (2001) Neuropeptides and neurotrophins in neonatal blood of children with autism or mental retardation. Ann Neurol 49: 597-606.
103. Connolly AM, Chez M, Streif EM, Keeling RM, Golumbek PT, et al. (2006) Brain-derived neurotrophic factor and autoantibodies to neural antigens in sera of children with autistic spectrum disorders, Landau-Kleffner syndrome, and epilepsy. Biol Psychiatry 59: 354-363.
104. Miyazaki K, Narita N, Sakuta R, Miyahara T, Naruse H, et al. (2004) Serum neurotrophin concentrations in autism and mental retardation: a pilot study. Brain Dev 26: 292-295.
105. Correia CT, Coutinho AM, Sequeira AF, Sousa IG, Lourenço Venda L, et al. (2010) Increased BDNF levels and NTRK2 gene association suggest a disruption of BDNF/TrkB signaling in autism. Genes Brain Behav 9: 841-848.
106. Garcia KL, Yu G, Nicolini C, Michalski B, Garzon DJ, et al. (2012) Altered balance of proteolytic isoforms of pro-brain-derived neurotrophic factor in autism. J Neuropathol Exp Neurol 71: 289-297.
107. Perry EK1, Lee ML, Martin-Ruiz CM, Court JA, Volsen SG, et al. (2001) Cholinergic activity in autism: abnormalities in the cerebral cortex and basal forebrain. Am J Psychiatry 158: 1058-1066.
108. Nishimura K, Nakamura K, Anitha A, Yamada K, Tsujii M, et al. (2007) Genetic analyses of the brain-derived neurotrophic factor (BDNF) gene in autism. Biochem Biophys Res Commun 356: 200-206.
109. Sheikh AM, Malik M, Wen G, Chauhan A, Chauhan V, et al. (2010) BDNF-Akt-Bcl2 antiapoptotic signaling pathway is compromised in the brain of autistic subjects. J Neurosci Res 88: 2641-2647.
110. Kelleher RJ, Bear MF (2008) The autistic neuron: troubled translation? Cell 135: 401-406.
111. Levitt P, Campbell DB (2009) The genetic and neurobiologic compass points toward common signaling dysfunctions in autism spectrum disorders. J Clin Invest 119: 747-754.
112. Troca-Marín JA, Alves-Sampaio A, Montesinos ML (2012) Deregulated mTOR-mediated translation in intellectual disability. Prog Neurobiol 96: 268-282.
113. Ehninger D, Silva AJ (2011) Rapamycin for treating Tuberous sclerosis and Autism spectrum disorders. Trends Mol Med 17: 78-87.
114. Gkogkas CG, Khoutorsky A, Ran I, Rampakakis E, Nevarko T, et al. (2013) Autism-related deficits via dysregulated eIF4E-dependent translational control. Nature 493: 371-377.
115. Menna E, Zambetti S, Morini R, Donzelli A, Disanza A, et al. (2013) Eps8 controls dendritic spine density and synaptic plasticity through its actin-capping activity. EMBO J 32: 1730-1744.
116. Li , Pozzo-Miller L (2014) BDNF deregulation in Rett syndrome. Neuropharmacology 76 Pt C: 737-746.
117. Zoghbi HY1, Bear MF (2012) Synaptic dysfunction in neurodevelopmental disorders associated with autism and intellectual disabilities. Cold Spring Harb Perspect Biol 4.
118. Kumar V, Zhang MX, Swank MW, Kunz J, Wu GY (2005) Regulation of dendritic morphogenesis by Ras-PI3K-Akt-mTOR and Ras-MAPK signaling pathways. J Neurosci 25: 11288-11299.
119. Tavazoie SF, Alvarez VA, Ridenour DA, Kwiatkowski DJ, Sabatini BL (2005) Regulation of neuronal morphology and function by the tumor suppressors Tsc1 and Tsc2. Nat Neurosci 8: 1727-1734.
120. Belichenko PV1, Oldfors A, Hagberg B, Dahlström A (1994) Rett syndrome: 3-D confocal microscopy of cortical pyramidal dendrites and afferents. Neuroreport 5: 1509-1513.
121. Belichenko PV, Wright EE, Belichenko NP, Masliah E, Li HH, et al. (2009) Widespread changes in dendritic and axonal morphology in Mecp2-mutant mouse models of Rett syndrome: evidence for disruption of neuronal networks. J Comp Neurol 514: 240-258.
122. Zhou Z1, Hong EJ, Cohen S, Zhao WN, Ho HY, et al. (2006) Brain-specific phosphorylation of MeCP2 regulates activity-dependent Bdnf transcription, dendritic growth, and spine maturation. Neuron 52: 255-269.
123. Bagni C, Greenough WT (2005) From mRNP trafficking to spine dysmorphogenesis: the roots of fragile X syndrome. Nat Rev Neurosci 6: 376-387.
124. Comery TA, Harris JB, Willems PJ, Oostra BA, Irwin SA, et al. (1997) Abnormal dendritic spines in fragile X knockout mice: maturation and pruning deficits. Proc Natl Acad Sci U S A 94: 5401-5404.
125. Irwin SA, Galvez R, Greenough WT (2000) Dendritic spine structural anomalies in fragile-X mental retardation syndrome. Cereb Cortex 10: 1038-1044.
126. Irwin SA, Patel B, Idupulapati M, Harris JB, Crisostomo RA, et al. (2001) Abnormal dendritic spine characteristics in the temporal and visual cortices of patients with fragile-X syndrome: a quantitative examination. Am J Med Genet 98: 161-167.
127. Nimchinsky EA, Oberlander AM, Svoboda K (2001) Abnormal development of dendritic spines in FMR1 knock-out mice. J Neurosci 21: 5139-5146.
128. Alvarez VA, Sabatini BL (2007) Anatomical and physiological plasticity of dendritic spines. Annu Rev Neurosci 30: 79-97.
129. Bourne JN, Harris KM (2008) Balancing structure and function at hippocampal dendritic spines. Annu Rev Neurosci 31: 47-67.
130. Cingolani LA, Goda Y (2008) Actin in action: the interplay between the actin cytoskeleton and synaptic efficacy. Nat Rev Neurosci 9: 344-356.
131. Kennedy MJ, Ehlers MD (2006) Organelles and trafficking machinery for postsynaptic plasticity. Annu Rev Neurosci 29: 325-362.
132. Nicolini C, Ahn Y, Michalski B, Rho JM, Fahnestock M1 (2015) Decreased mTOR signaling pathway in human idiopathic autism and in rats exposed to valproic acid. Acta Neuropathol Commun 3: 3.
133. Weston MC, Chen H, Swann JW (2012) Multiple roles for mammalian target of rapamycin signaling in both glutamatergic and GABAergic synaptic transmission. J Neurosci 32: 11441-11452.
134. Centonze, Rossi S, Mercaldo V, Napoli I, Ciotti MT, et al. (2008) Abnormal striatal GABA transmission in the mouse model for the fragile X syndrome. Biol Psychiatry 63: 963-973.
135. Curia G, Papouin T, Séguéla P, Avoli M (2009) Downregulation of tonic GABAergic inhibition in a mouse model of fragile X syndrome. Cereb Cortex 19: 1515-1520.
136. Selby L, Zhang C, Sun QQ (2007) Major defects in neocortical GABAergic inhibitory circuits in mice lacking the fragile X mental retardation protein. Neurosci Lett 412: 227-232.
137. Chao HT, Chen H, Samaco RC, Xue M, Chahrour M, et al. (2010) Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. Nature 468: 263-269.
138. Medrihan L, Tantalaki E, Aramuni G, Sargsyan V, Dudanova I, et al. (2008) Early defects of GABAergic synapses in the brain stem of a MeCP2 mouse model of Rett syndrome. J Neurophysiol 99: 112-121.

139. Sato A, Kasai S, Kobayashi T, Takamatsu Y, Hino O, et al. (2012) Rapamycin reverses impaired social interaction in mouse models of tuberous sclerosis complex. Nat Commun 3: 1292.
140. Zhou J, Blundell J, Ogawa S, Kwon CH, Zhang W, et al. (2009) Pharmacological inhibition of mTORC1 suppresses anatomical, cellular, and behavioral abnormalities in neural-specific Pten knock-out mice. J Neurosci 29: 1773-1783.
141. Tropea D, Giacometti E, Wilson NR, Beard C, McCurry C, et al. (2009) Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice. Proc Natl Acad Sci U S A 106: 2029-2034.
142. Ricciardi S, Boggio EM, Grosso S, Lonetti G, Forlani G, et al. (2011) Reduced AKT/mTOR signaling and protein synthesis dysregulation in a Rett syndrome animal model. Hum Mol Genet 20: 1182-1196.
143. Schmid DA, Yang T, Ogier M, Adams I, Mirakhur Y, et al. (2012) A TrkB small molecule partial agonist rescues TrkB phosphorylation deficits and improves respiratory function in a mouse model of Rett syndrome. J Neurosci 32: 1803-1810.
144. Chen J, Alberts I2, Li X3 (2014) Dysregulation of the IGF-I/PI3K/AKT/mTOR signaling pathway in autism spectrum disorders. Int J Dev Neurosci 35: 35-41.
145. Khwaja OS, Ho E, Barnes KV, O'Leary HM, Pereira LM, et al. (2014) Safety, pharmacokinetics, and preliminary assessment of efficacy of mecasermin (recombinant human IGF-1) for the treatment of Rett syndrome. Proc Natl Acad Sci U S A 111: 4596-4601.
146. Amaral DG, Schumann CM, Nordahl CW (2008) Neuroanatomy of autism. Trends Neurosci 31: 137-145.
147. Allison T, Ginter H, McCarthy G, Nobre AC, Puce A, et al. (1994) Face recognition in human extrastriate cortex. J Neurophysiol 71: 821-825.
148. Boucher J, Lewis V (1992) Unfamiliar face recognition in relatively able autistic children. J Child Psychol Psychiatry 33: 843-859.
149. Grelotti DJ, Klin AJ, Gauthier I, Skudlarski P, Cohen DJ, et al. (2005) fMRI activation of the fusiform gyrus and amygdala to cartoon characters but not to faces in a boy with autism. Neuropsychologia 43: 373-385.
150. Kanwisher N, McDermott J, Chun MM (1997) The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci 17: 4302-4311.
151. Pierce K, Müller RA, Ambrose J, Allen G, Courchesne E (2001) Face processing occurs outside the fusiform 'face area' in autism: evidence from functional MRI. Brain 124: 2059-2073.
152. Schultz RT, Gauthier I, Klin A, Fulbright RK, Anderson AW, et al. (2000) Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. Arch Gen Psychiatry 57: 331-340.
153. Menna E, Disanza A, Cagnoli C, Schenk U, Gelsomino G, et al. (2009) Eps8 regulates axonal filopodia in hippocampal neurons in response to brain-derived neurotrophic factor (BDNF). PLoS Biol 7: e1000138.
154. Lin YC, Koleske AJ (2010) Mechanisms of synapse and dendrite maintenance and their disruption in psychiatric and neurodegenerative disorders. Annu Rev Neurosci 33: 349-378.
155. Cao C, Rioult-Pedotti MS, Migani P, Yu CJ, Tiwari R, et al. (2013) Impairment of TrkB-PSD-95 signaling in Angelman syndrome. PLoS Biol 11: e1001478.
156. Löscher W (2002) Basic pharmacology of valproate: a review after 35 years of clinical use for the treatment of epilepsy. CNS Drugs 16: 669-694.
157. Emrich HM, von Zerssen D, Kissling W, Möller HJ, Windorfer A (1980) Effect of sodium valproate on mania. The GABA-hypothesis of affective disorders. Arch Psychiatr Nervenkr (1970) 229: 1-16.
158. Lambert PA, Carraz G, Borselli S, Bouchardy M (1975) [Dipropylacetamide in the treatment of manic-depressive psychosis]. Encephale 1: 25-31.
159. Phiel CJ, Zhang F, Huang EY, Guenther MG, Lazar MA, et al. (2001) Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. J Biol Chem 276: 36734-36741.
160. Chomiak T, Hu B (2013) Alterations of neocortical development and maturation in autism: insight from valproic acid exposure and animal models of autism. Neurotoxicol Teratol 36: 57-66.
161. Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, et al. (2013) Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA 309: 1696-1703.
162. Christianson AL, Chesler N, Kromberg JG (1994) Fetal valproate syndrome: clinical and neuro-developmental features in two sibling pairs. Dev Med Child Neurol 36: 361-369.
163. Rodier PM, Ingram JL, Tisdale B, Nelson S, Romano J (1996) Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. J Comp Neurol 370: 247-261.
164. Mehta MV1, Gandal MJ, Siegel SJ (2011) mGluR5-antagonist mediated reversal of elevated stereotyped, repetitive behaviors in the VPA model of autism. PLoS One 6: e26077.
165. Roullet FI, Wollaston L, Decatanzaro D, Foster JA (2010) Behavioral and molecular changes in the mouse in response to prenatal exposure to the anti-epileptic drug valproic acid. Neuroscience 170: 514-522.
166. Schneider T, PrzewÅ‚ocki R (2005) Behavioral alterations in rats prenatally exposed to valproic acid: animal model of autism. Neuropsychopharmacology 30: 80-89.
167. Kataoka S1, Takuma K, Hara Y, Maeda Y, Ago Y, et al. (2013) Autism-like behaviours with transient histone hyperacetylation in mice treated prenatally with valproic acid. Int J Neuropsychopharmacol 16: 91-103.
168. Ingram JL, Peckham SM, Tisdale B, Rodier PM (2000) Prenatal exposure of rats to valproic acid reproduces the cerebellar anomalies associated with autism. Neurotoxicol Teratol 22: 319-324.
169. Rodier PM, Ingram JL, Tisdale B, Croog VJ (1997) Linking etiologies in humans and animal models: studies of autism. Reprod Toxicol 11: 417-422.
170. Bringas ME, Carvajal-Flores F, López-Ramírez TA, Atzori M, Flores G (2013) Rearrangement of the dendritic morphology in limbic regions and altered exploratory behavior in a rat model of autism spectrum disorder. Neuroscience 241: 170-187.
171. Rinaldi T, Kulangara K, Antoniello K, Markram H (2007) Elevated NMDA receptor levels and enhanced postsynaptic long-term potentiation induced by prenatal exposure to valproic acid. Proc Natl Acad Sci U S A 104: 13501-13506.
172. Walcott EC, Higgins EA, Desai NS (2011) Synaptic and intrinsic balancing during postnatal development in rat pups exposed to valproic acid in utero. J Neurosci 31: 13097-13109.
173. Kolozsi E, Mackenzie RN, Roullet FI, deCatanzaro D, Foster JA (2009) Prenatal exposure to valproic acid leads to reduced expression of synaptic adhesion molecule neuroligin 3 in mice. Neuroscience 163: 1201-1210.
174. Rinaldi T, Silberberg G, Markram H (2008) Hyperconnectivity of local neocortical microcircuitry induced by prenatal exposure to valproic acid. Cereb Cortex 18: 763-770.
175. Rinaldi T, Perrodin C, Markram H (2008) Hyper-connectivity and hyper-plasticity in the medial prefrontal cortex in the valproic Acid animal model of autism. Front Neural Circuits 2: 4.
176. Rubenstein JL, Merzenich MM (2003) Model of autism: Increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav 2: 255-267.
177. Gogolla N, Leblanc JJ, Quast KB, Südhof TC, Fagiolini M, et al. (2009) Common circuit defect of excitatory-inhibitory balance in mouse models of autism. J Neurodev Disord 1: 172-181.
178. Schneider T, Turczak J, PrzewÅ‚ocki R (2006) Environmental enrichment reverses behavioral alterations in rats prenatally exposed to valproic acid: issues for a therapeutic approach in autism. Neuropsychopharmacology 31: 36-46.
179. Ahn Y, Narous M, Tobias R, Hu B, Rho JM (2012) Alterations in social behavior and mTOR signaling in the valproic acid-induced model of autism spectrum disorder, Program No. 861.21. 2012 Neuroscience Meeting Planner. Society for Neuroscience, New Orleans, LA, Online.

180. Chomiak T, Karnik V, Block E, Hu B (2010) Altering the trajectory ofearly postnatal cortical development can lead to structural and behavioural features of autism. BMC Neurosci 11: 102.