Functional Consequences of Mutations in Postsynaptic Scaffolding Proteins and Relevance to Psychiatric Disorders

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Abstract

Functional studies on postsynaptic scaffolding proteins at excitatory synapses have revealed a plethora of important roles for synaptic structure and function. In addition, a convergence of recent in vivo functional evidence together with human genetics data strongly suggest that mutations in a variety of these postsynaptic scaffolding proteins may contribute to the etiology of diverse human psychiatric disorders such as schizophrenia, autism spectrum disorders, and obsessive-compulsive spectrum disorders. Here we review the most recent evidence for several key postsynaptic scaffolding protein families and explore how mouse genetics and human genetics have intersected to advance our knowledge concerning the contributions of these important players to complex brain function and dysfunction.

Contents

PSD: postsynaptic density

INTRODUCTION

The Anatomy of the Postsynaptic Specialization at Excitatory Synapses

The chemical synapse is a microscopic physical structure that conveys electrical signals from presynaptic to postsynaptic neurons within brain circuits by means of chemical neurotransmitter release and action. Both excitatory and inhibitory neurotransmitter release act in concert under constant fine-tuning to orchestrate the flow of information processing in the nervous system. Most excitatory synapses are formed between presynaptic boutons loaded with glutamate-filled synaptic vesicles and tightly apposed protrusions of postsynaptic receptor-laden dendritic spines.

The dendritic spine is a highly specialized structure that is both complex and elegant. Electron microscopy images of excitatory synapses prominently feature a dense proteinacious matrix at the tip of the spine head immediately underlying the postsynaptic membrane face. This protein mesh is called the postsynaptic density (PSD), and decades of research using primarily biochemical and molecular cloning methods have led to the identification of many prominent PSD constituents. The PSD contains many distinct classes of proteins, including neurotransmitter receptors, cell adhesion molecules, ion channels, signaling molecules, and scaffolding proteins (**Figure 1**). The dynamic nature and precise topographical organization of these components give rise to a supramolecular signal-processing machine.

Scaffolding Proteins Constitute the Structural Core of the Postsynaptic Density

Scaffolding proteins are extremely abundant in the PSD, both in terms of absolute protein copy numbers and the distinct types of scaffolding proteins that have been described to date (Kim & Sheng 2004, Sheng & Hoogenraad 2007). The most well-studied postsynaptic scaffolding proteins include members of the

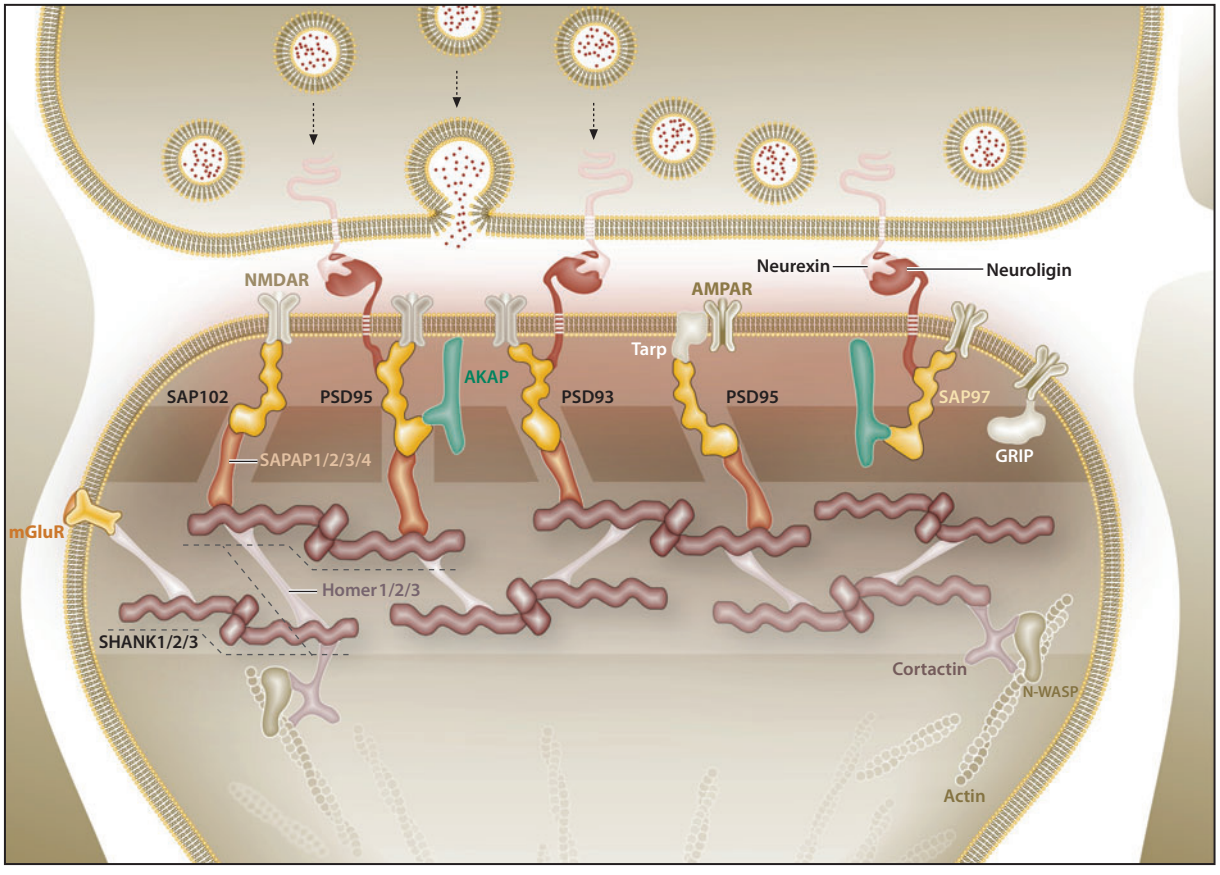

Figure 1

Scaffolding protein networks at the postsynaptic density (PSD). Schematic of the major family members of PSD scaffolding proteins at excitatory synapses. Current information from structural studies suggests that Shank protein can dimerize through C-terminal sterile alpha motif (SAM) domain–SAM domain interaction and form a supramolecular polymeric network with Homer tetramers. This complex may connect to perisynaptic mGluRs and to synaptic NMDA and AMPA-type ionotropic glutamate receptors through the PSD95 and SAPAP (SAP90/PSD95-associated protein) family of proteins. The Shank/Homer platform may also provide key connection points to the spine actin cytoskeleton. A-kinase anchoring protein (AKAP) is another important protein that can anchor kinases and phosphatases (not shown here) in the vicinity of synaptic receptors and ion channels.

PSD95 family, select members of the A-kinase anchoring protein (AKAP) family, the Homer family, the SAP90/PSD95-associated protein (SAPAP) family, and the SH3 and multiple ankyrin repeat domain (Shank) family. Scaffolding-protein families are generally defined by a highly conserved organization of domains for protein-protein interactions, and it is the unique combinations and properties of these domains that impart a specificity of protein-protein interactions exhibited by each of these families (**Figure 2**). Furthermore, postsynaptic scaffolding proteins can interact with multiple binding partners simultaneously to physically link PSD components and, thus, can be viewed as the master organizers within this specialized structure.

Here we aim to highlight evidence from the recent literature concerning the in vivo functional roles served by the major postsynaptic scaffolding protein families. We further examine findings that have emerged from human genetics investigations exploring variations in genes that encode postsynaptic scaffolding

AKAP: A-kinase anchoring protein

SAPAP: SAP90/PSD95-associated protein

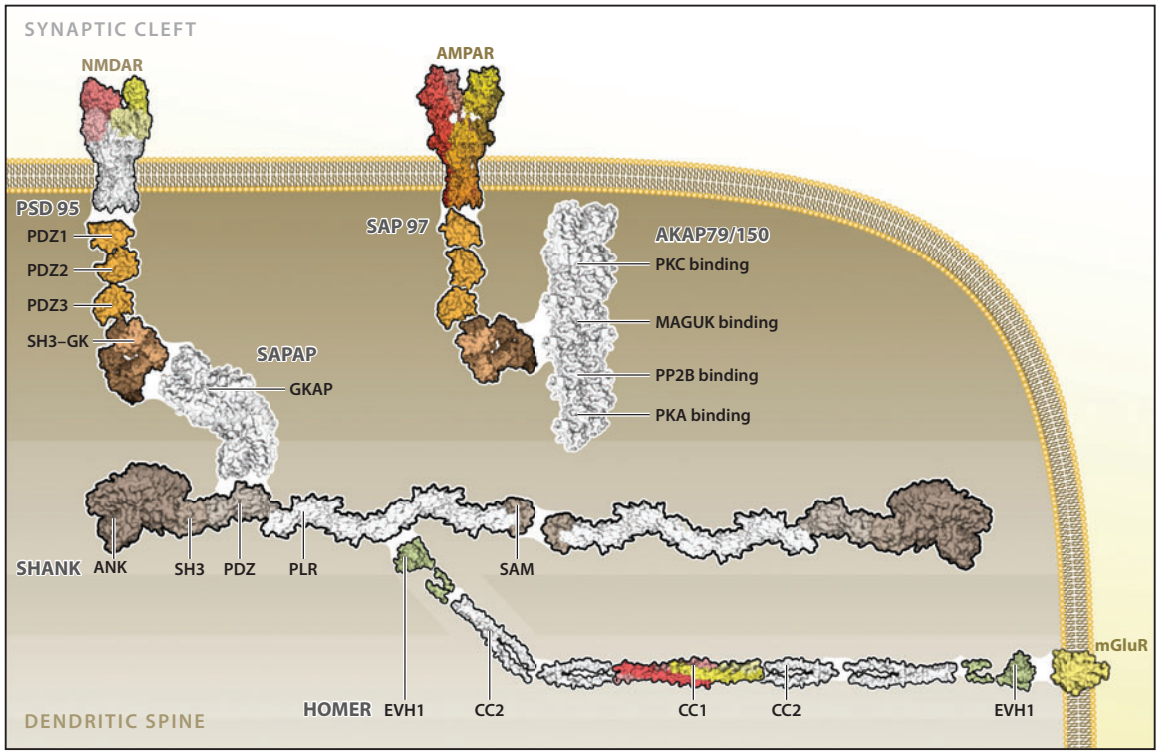

Figure 2

Physical interactions via discrete binding domains in postsynaptic density (PSD) scaffolding proteins. Representation of the known atomic structures from crystallized domains in key PSD scaffolding proteins, highlighting interactions at known binding sites. For simplicity, protein domains that have not been resolved at the atomic level are displayed in white. Represented domains include the PDZ and SH3 domains of PSD95 and Shank family proteins, the GK domain in PSD95 family proteins, the Ank and SAM domains in Shank family proteins, and the EVH1 and coiled-coil (CC) domains in Homer family proteins (information on these structures was obtained through the RCSB Protein Data Bank **http://www.pdb.org**).

proteins in relation to psychiatric disorders (see Diversity of Human Psychiatric Disorders, sidebar below). More comprehensive coverage of other known PSD scaffolding molecules, particularly with respect to structural considerations, can be found elsewhere (Chen et al. 2008, Kim & Sheng 2004, Sheng & Hoogenraad 2007).

PSD95/MAGUK FAMILY

Membrane-associated guanylate kinase (MAGUK) proteins form a superfamily of scaffolding proteins present in several organisms and serving various cellular roles. Here, special consideration is given to the commonly defined PSD95 family of proteins, a subfamily of MAGUKs comprised of synapse-associated protein (SAP)102, SAP97, PSD93, and PSD95. These MAGUKs are orthologs of *Drosophila DLG* (discs large), the first cloned MAGUK (Woods & Bryant 1991).

The PSD95 protein was among the first components to be identified as a part of the PSD (Sampedro et al. 1981). Structurally, members of the PSD95 family share several common protein-protein interaction domains. From the N to C terminus these include an L27 domain, three PDZ domains (PDZ1, PDZ2, and PDZ3, termed after their occurrence in three related MAGUKs, PSD95, Dlg, and ZO-1), an SH3 domain (SRC homology 3 domain), and a

MAGUK: membrane-associated guanylate kinase

Ortholog: genes in different species that evolved from a common ancestral gene and have retained the same function

DLG: discs large

PDZ domain: PSD95, Dlg, and ZO-1 domain

C-terminal catalytically inactive guanylate kinase-like (GK) domain (Kuhlendahl et al. 1998).

PDZ domains are found in a wide variety of eukaryotic proteins and display considerable sequence variation, presumably underlying functional diversity and binding specificities (Sheng & Sala 2001). The majority of known PDZ domains interact with a canonical C-terminal sequence found in the binding partners. Some of the most notable binding partners to the first two PDZ domains of PSD95 include the Shaker-type K^+ channels and NR2A subunits of the N-methyl-D-aspartate type glutamate receptor (NMDAR), both through C-terminal PDZ binding motifs (Kim et al. 1995, Kornau et al. 1995). Neuroligins, a family of cell adhesion molecules located at synapses, also bind to the third PDZ domain in PSD95 through a C-terminal PDZ motif (Irie et al. 1997). The demonstrated interactions were later expanded to include several members of the PSD95 family: PDZ1 and PDZ2 from SAP97 emulate the NR2A/PSD95 interaction, whereas in SAP102 all three PDZ domains can bind to the NR2B subunit of the NMDAR. Finally, PSD93 also interacts and promotes the clustering of NMDAR subunits in heterologous cells (Kim et al. 1996, Niethammer et al. 1996). PDZ domains are also responsible for the regulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid type glutamate receptors (AMPARs). SAP97 directly interacts with the GluR1 subunit of the AMPAR and is involved in the trafficking of these channels (Leonard et al. 1998). However, the interaction between GluR subunits and PSD95 is indirectly mediated through transmembrane AMPAR regulatory proteins such as Stargazin (Chen et al. 2000, Schnell et al. 2002, Tomita et al. 2004).

In PSD95, both SH3 and GK domains bind to and promote clustering of the Kainate-type ionotropic glutamate receptors (Garcia et al. 1998). These domains also exhibit intramolecular SH3-GK self-binding (McGee & Bredt 1999), suggesting the possibility that SH3 domains in PSD95 family proteins bind with partners outside of the archetypical SH3 interactions with proline-rich motifs. A prominent binding partner of the GK domain is the SAPAP family of scaffolding proteins (Kim et al. 1997, Satoh et al. 1997, Takeuchi et al. 1997). An additional partner to the GK domain of PSD95 is SPAR (Spine-associated RapGAP). This protein regulates spine morphology and displays actin-reorganization activity (Pak et al. 2001).

DIVERSITY OF HUMAN PSYCHIATRIC DISORDERS

Autism spectrum disorders (ASDs): a group of neurodevelopmental disorders sharing similar core features such as social impairments, language or communication defects, and repetitive behaviors. Examples include autism, Rett syndrome, and Asperger syndrome.

Obsessive-compulsive spectrum disorders: a group of psychiatric disorders sharing core features such as recurrent obsessions, increased anxiety, and compulsive repetitive behaviors. Examples include obsessive-compulsive disorder (OCD), compulsive hair-pulling/Trichotillomania (TTM), Tourette syndrome, and body dysmorphic disorder.

Mood disorders: a group of psychiatric disorders in which the primary symptom is extreme disturbance in mood, such as experiencing either a limited or exaggerated range of feelings. The most prominent examples include major depression and bipolar disorder.

Schizophrenia: a psychiatric disorder characterized by a pervasive disruption in the normal balance of thought and emotion. Symptoms can be divided into three clusters: positive symptoms (hallucinations, delusions, or disorganized speech and/or thoughts), negative symptoms (lack of pleasure or lack of affect), and cognitive symptoms (attention or working memory deficits).

Mutational Analysis of PSD95 Family Function In Vivo

Manipulating the expression levels of PSD95 family proteins has yielded several insights into the role these proteins play at the synapse. Overexpression of PSD95 in dissociated neuron cultures and organotypic slices causes an enhancement of AMPAR-mediated, but

GK domain: guanylate kinase-like domain

NMDAR: N-methyl-D-aspartate receptor

AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

Copy number variations (CNVs): submicroscopic unbalanced structural genomic variations ranging from the kilobase to megabase scale, potentially giving rise to increased or decreased gene copy numbers

not NMDAR-mediated synaptic currents (El-Husseini et al. 2000, Schnell et al. 2002). Conversely, knockdown of PSD95 leads to decreased AMPAR-mediated synaptic currents (Ehrlich et al. 2007). Manipulations of PSD93 and SAP102 protein levels led to similar functional alterations (Elias et al. 2006). Furthermore, the in vivo role of PSD95 family members was probed by the analysis of genetically modified mice harboring mutations in these genes. From these, SAP97 mutant mice are less amenable for study using homozygous germline deletion, given that this perturbation results in perinatal lethality (Caruana & Bernstein 2001). By contrast, SAP102 (Cuthbert et al. 2007), PSD93 (McGee et al. 2001), and PSD95 (Beique et al. 2006, Migaud et al. 1998, Yao et al. 2004) mutant animals manifest only subtle phenotypes. Perhaps the most salient findings have come from a distinct line of PSD95 mutant mice that display augmented sensitivity to the locomotor-stimulating effects of cocaine and enhanced cortical-accumbal long-term potentiation but an absence of cocaine-induced behavioral plasticity (Yao et al. 2004). More recently, further research with PSD95 mutant mice revealed that these animals display several behavioral deficits relevant to autism spectrum disorders (ASDs) (Feyder et al. 2010). Nevertheless, the lack of obvious overt synaptic deficits in PSD95 and PSD93 mice suggests functional redundancy and/or compensation among PSD95 family members. To elucidate this, a *tour de force* study achieved a functional ablation of PSD95, PSD93, and SAP102 by combining PSD95/PSD93 double-knockout animals with SAP102 knockdown (Elias et al. 2006). This work illustrated how synaptic specificity and developmental regulation of AMPARs is influenced by PSD95 and PSD93 in nonoverlapping populations of mature synapses, whereas, SAP102 plays an important role at immature synapses. Moreover, SAP102 is upregulated in response to PSD95/PSD93 deletion, thus contributing to the remarkable functional redundancy within this protein family (Elias et al. 2006). More broadly, this work highlights the difficulties encountered in trying to assess the in vivo functional roles of particular proteins when closely related genes are expressed (or become expressed) in partially overlapping cell populations.

Human Molecular Genetics Data for PSD95 Gene Family

Several groups have reported altered levels of PSD95 family proteins in patients afflicted with mood disorders or schizophrenia (Feyissa et al. 2009, Karolewicz et al. 2009, Kristiansen et al. 2006, Toro & Deakin 2005, Toyooka et al. 2002). Although these data hint at the possibility that altered expression of PSD95 family proteins may play a role in human psychiatric disorders, they in no way address whether such changes are an epiphenomena or if they are in some way causative. Nevertheless, further converging evidence has come from studies examining the involvement of the *DLG1-4* genes (*DLG1*/SAP97, *DLG2*/PSD93, *DLG3*/SAP102, *DLG4*/PSD95) in psychiatric disorders. Of particular note is the association of *DLG1* with the 3q29 microdeletion syndrome—a condition characterized by mild-to-moderate mental retardation, dysmorphic facial features, ataxia, and autism (Willatt et al. 2005). This microdeletion leads to the elimination of PAK2 and DLG1, which purportedly underlie both dysmorphic and neurological symptoms (Willatt et al. 2005). Furthermore, *DLG1* copy number variations (CNVs) have been identified in patients diagnosed with schizophrenia (Magri et al. 2010, Sato et al. 2008). *DLG3* has been strongly implicated in X-linked mental retardation (Tarpey et al. 2004), whereas *DLG4* was recently linked to autistic behaviors and schizophrenia (Cheng et al. 2010, Feyder et al. 2010). Together, these multiple lines of evidence support the hypothesis that the various members of the PSD95 family of proteins collectively contribute toward the healthy functioning of the mammalian brain.

AKAP FAMILY

The A-kinase anchoring protein (AKAP) family is comprised of a broad collection of proteins

defined by the ability to anchor protein kinase A (PKA) (Wong & Scott 2004). As such, AKAPs serve critical roles in the spatial and temporal regulation of PKA activity and intracellular signaling cascades. The AKAP family members are classified according to this PKA binding ability rather than on sequence similarity; therefore, AKAPs are structurally very diverse.

The *AKAP5* gene encodes AKAP5, commonly known as AKAP79 in humans and AKAP150 in rodents (jointly called AKAP79/150). In the brain, AKAP79/150 is highly enriched in the PSD of excitatory synapses (Carr et al. 1992) by virtue of an N-terminal polybasic membrane-targeting region (Dell'Acqua et al. 1998). AKAP79/150 also contains distinct sequences that mediate anchoring of the protein kinases PKA and PKC and the protein phosphatase PP2B (also called calcineurin) (Carr et al. 1992, Coghlan et al. 1995, Klauck et al. 1996). In addition to the anchoring of these important signaling molecules, AKAP79/150 interacts directly with the SH3 and GK domains of PSD95 and SAP97 (Colledge et al. 2000). Importantly, PSD95 and SAP97 have specific roles in regulating synaptic localization of NMDARs and AMPARs, respectively. Thus, distinct complexes containing AKAP79/150-PSD95-NMDAR and AKAP79/150-SAP97-AMPAR exist within the PSD region of excitatory synapses (Colledge et al. 2000), providing a molecular basis for differential regulation of the major classes of ionotropic glutamate receptors via scaffolding of unique signaling complexes to different target receptors. AKAP79/150 also interacts directly with and functionally regulates a variety of other ion channels and G protein–coupled receptors (Dart & Leyland 2001, Hall et al. 2007, Hoshi et al. 2003, Lin et al. 2010, Oliveria et al. 2007).

An influential early study in cultured hippocampal neurons showed that cell-wide disruption of PKA binding to AKAPs by an inhibitory peptide (Ht31) led to run-down of evoked AMPAR-mediated currents in a manner identical to infusion of a specific PKA inhibitory peptide (Rosenmund et al. 1994). Ht31 infusion also caused long-term reductions in surface AMPAR subunit GluR1 expression in cultured hippocampal neurons, and it occluded long-term depression evoked by electrical stimulation in acute hippocampal slices (Snyder et al. 2005). However, Ht31 broadly interferes with PKA binding to all AKAPs; therefore, subsequent work was necessary to provide specific evidence for the involvement of AKAP79/150 in the modulation of AMPAR function.

Two independent studies used an elegant molecular replacement strategy (depletion of the endogenous AKAP79/150 followed by expression of mutant versions) to show convincingly that expression of PP2B-binding-deficient AKAP79/150 (AKAP79/150ΔPP2B) prevented agonist-induced downregulation of AMPAR currents in cultured hippocampal neurons (Hoshi et al. 2005) and abolished NMDAR-dependent long-term depression in hippocampal slices (Jurado et al. 2010). These results fit well with another report showing that overexpression of AKAP79/150ΔPP2B prevented NMDA-triggered AMPAR endocytosis in cultured hippocampal neurons (Bhattacharyya et al. 2009).

Overall, the anchoring of PKA and PP2B through AKAP79/150 in the PSD region seems to exert influences on AMPAR function and plasticity. These data are largely consistent with the hypothesis that AMPARs are dynamically regulated by phosphorylation and dephosphorylation of GluR1 subunits, mediated by a functional balance of signaling from AKAP79/150-anchored PKA versus PP2B near the receptor substrates. Exactly how anchoring to AKAP79/150 influences PKA and PP2B activities in this context and the relative importance of each to discrete synaptic functions is an open question.

Mutational Analysis of AKAP79/150 Function In Vivo

Two independent laboratories have recently generated *AKAP150* null mice (Hall et al. 2007, Tunquist et al. 2008), providing ample opportunities to investigate the

Null mutation: a genetic lesion that ablates gene function completely, most commonly through the functional disruption of mRNA or protein production

Knock-in mutation: targeted manipulation in the mouse genome aimed at substituting an endogenous sequence with an altered sequence

physiological functions of this scaffolding protein. Both null mouse lines are viable and fertile, and both groups demonstrated that AKAP150 is the major AKAP in the brain responsible for proper anchoring of PKA within dendritic regions, consistent with the PSD localization of AKAP150. One line also has deficits in motor coordination and strength, consistent with the expression of AKAP150 in the cerebellum (Tunquist et al. 2008).

A third AKAP150 mutant mouse line harboring a knock-in mutation has also been generated by introducing a premature stop codon that results in the deletion of the last 36 amino acids from the C terminus of the AKAP150 protein and fully eliminates PKA anchoring by AKAP150 (i.e., AKAP150ΔPKA), hence the term D36 mice (Lu et al. 2007). D36 mice and *AKAP150* null mice both showed abnormally increased numbers of dendritic spines in vivo and an increased number of functional excitatory synapses in acute hippocampal slices (Lu et al. 2011). These changes are apparent in the early postnatal and juvenile stages but do not persist into adulthood. D36 and *AKAP150* null mice also had larger and more frequent inhibitory synaptic events in acute brain slices from juveniles, which was suggested to be a compensatory change to counteract increased excitatory synaptic function. These findings point to a role of AKAP150-anchored PKA in limiting dendritic spine density in vivo, although these data seem at odds with a portion of earlier results obtained using cultured hippocampal neurons (Robertson et al. 2009). The functions assessed in vivo using mutant mice may have more physiological relevance, although in some cases the potentially confounding influence of compensatory changes may be less of a factor using acute manipulations in vitro.

A surprising finding from multiple studies comparing the *AKAP150* null and D36 mice is that synaptic plasticity and behavioral phenotypes are generally more severe in D36 mice than in the constitutive null mice (Lu et al. 2007, Weisenhaus et al. 2010). For example, long-term potentiation was impaired in young adult D36 mice and long-term depression was impaired in juvenile D36 mice, but no deficits in either form of long-term plasticity were detected in the null mice (but see also Tunquist et al. 2008). Furthermore, reversal learning was impaired in D36 mice but not in null mice. The unique deficits in the D36 mice may partially be explained by the fact that AKAP79/150 normally binds with both PKA and PP2B at synapses; thus, incorporating mutant AKAP150ΔPKA that retains PP2B binding at the PSD may profoundly alter the signaling balance more potently in D36 mice than in the *AKAP150* null mice. The AKAP150ΔPKA deletion also appears to cover the reported binding site for L-type calcium channels in the distal C-terminal portion of AKAP150 (Oliveria et al. 2007), which may further complicate matters in the D36 mice, particularly with respect to the contribution of these channels to postsynaptic calcium entry during synaptic activity and plasticity. Finally, given the recent claim that AKAP150ΔPP2B mutant mice have been established (Sanderson & Dell'Acqua 2011), the detailed characterization of these mutant mice as measured against D36 mice will be of great interest.

Human Molecular Genetics Data on AKAP5

One study reported CNVs in bipolar disorder and schizophrenia cases that mapped to loci containing brain-expressed genes with known roles in neuronal function, including *AKAP5* (Wilson et al. 2006). The copy number increase in *AKAP5* was validated in a single bipolar-disorder sample. A second cohort of 60 samples (15 bipolar disorder, 15 schizophrenia, 15 major depression, and 15 healthy control) was directly tested for CNVs at the identified loci by quantitative PCR. This replication phase revealed three cases with copy number increases in *AKAP5* (one bipolar disorder, one schizophrenia, and one major depression) with no aberrations detected in controls.

A subsequent study called into question the reliability of the high-throughput methodology and provided evidence that the prior study may have generated false-positive CNV results (Sutrala et al. 2007). Two alternative contrasting methodologies were used to test for CNVs in schizophrenia cases for the previously implicated genes. No CNVs in cases or control samples were found for any of the genes examined, including *AKAP5*.

HOMER FAMILY

The Homer family in mammalian species consists of the *Homer1*, *Homer2*, and *Homer3* genes. A wide variety of alternatively spliced transcriptional variants of Homer family members have been described (Shiraishi-Yamaguchi & Furuichi 2007). A short Homer1a form was first identified in the hippocampal brain region as an immediate early gene product that was rapidly and transiently upregulated in neurons in response to seizure (Brakeman et al. 1997). The remaining Homer forms were subsequently identified based on sequence homology with Homer1a and, in particular, by the presence of a conserved N-terminal EVH1 domain found in all family members. Notably, many other family members have a C-terminal coiled-coil domain that is absent in Homer1a; as such, these are referred to as long Homer forms. The predominant long-protein forms isolated from the brain are Homer1b/c, Homer2a/b, and Homer3a/b (Shiraishi-Yamaguchi & Furuichi 2007). The coiled-coil domain mediates multimerization of long Homers into linear tetrameric assemblies in vitro (Hayashi et al. 2006), whereas EVH1 domain mediates interactions with proline-rich motifs. Several important Homer binding proteins have been identified, including group 1 metabotropic glutamate receptors (mGluR1α/mGluR5), IP3 receptors, Ryanodine receptors, TRPC channels, Dynamin3, and Shank proteins (Brakeman et al. 1997; Tu et al. 1998, 1999; Yuan et al. 2003).

The long Homer proteins are found at the PSD of excitatory synapses (Xiao et al. 1998) where they serve as scaffolding proteins linking surface receptors to intracellular signaling pathways, most notably, intracellular calcium signaling (Sala et al. 2005). The multimerization of long Homers into tetramers may be particularly important for linking together a dense matrix of Shanks that form a core structural platform of the PSD specialization (Hayashi et al. 2009). Disruption of tetramerization in neurons using a Homer1b dimeric mutant greatly reduced spine localization of Homer, Shank, and PSD95. Furthermore, these changes correlated with reduced glutamatergic postsynaptic currents, indicating a concerted role of long Homer tetramerization in controlling the structure and function of the postsynaptic compartment. As such, long Homers may be considered the "glue" in the dense Shank network of the PSD, and the tail-to-tail tetrameric arrangement of long Homers with pairs of EVH1 ligand-binding domains at each end can equally well explain an additional role of physically and functionally coupling a range of spatially segregated binding partners in perisynaptic regions.

The relationship between the constitutively expressed long Homer forms and activity-inducible Homer1a at the synapse has received much attention. The widely adopted view is that activity-inducible Homer1a may disrupt the assembly of long Homer scaffolding complexes through a competitive EVH1 domain-binding model in response to dynamic neuronal activity. This inferred dominant-negative regulatory mechanism has been demonstrated by direct experimental evidence in a variety of different contexts (Kammermeier 2008; Sala et al. 2001, 2003; Tappe et al. 2006; Tu et al. 1998). Other functional roles for activity-inducible Homer1a at the synapse have also been described (though not mutually exclusive), such as inducing conformation changes in target receptors to influence receptor activity (Ango et al. 2001, Hu et al. 2010), enabling functional crosstalk between metabotropic and ionotropic glutamate receptor classes at the synapse (Bertaso et al. 2010), and synaptic tagging in persistent forms of synaptic plasticity (Okada et al. 2009).

Synaptic tagging: a hypothetical construct explaining the molecular basis behind conversion of temporary synaptic changes into persistent or "long-term" plasticity at specific synaptic sites

Synaptic scaling: a "global" form of homeostatic plasticity where synaptic strength is increased or decreased to counter persistent changes in neuronal activity

Single nucleotide polymorphisms (SNPs): DNA sequence variations at a single nucleotide position within an individual's genome

GKAP: guanylate kinase–associated protein

Mutational Analysis of Homer Function In Vivo

Homer1 null mice have broad behavioral abnormalities consistent with other animal models of schizophrenia (Szumlinski et al. 2005). Notably, the *Homer1* null allele eliminates both the long and short forms of Homer1 that mediate discrete and, in some cases, opposing functions. This issue largely precludes detailed investigation into the precise roles of Homer1a and Homer1b/c in vivo using these mice. Hu et al. (2010) recently reported a selective Homer1a-deficient mouse and provided convincing evidence that Homer1a is largely indispensable for the induction of homeostatic synaptic scaling. Upregulation of Homer1a facilitated agonist-independent signaling at group 1 mGluRs, which was a requisite step leading to downregulation of synaptic AMPARs.

Both *Homer1* null and *Homer2* null (but not *Homer3* null) mice exhibit behavioral sensitization to the psychostimulant cocaine in the absence of prior cocaine exposure (Szumlinski et al. 2004). Furthermore, the behavioral and neurochemical profiles of *Homer2* null mice closely mirror the numerous changes induced by withdrawal from repeated cocaine administration. Viral expression of Homer2b in the striatum normalized the behaviors of the *Homer2* null mice, thus implicating disruption of striatal Homer2 in enabling cocaine-induced neuroplasticity. How Homer1 and Homer2 are mechanistically coupled to the efficacy of cocaine action in the brain remains unresolved.

Long Homer forms are also expressed at low levels in non-neuronal tissues, and analysis of Homer function in pancreatic acinar cells using *Homer2* and *Homer3* null mice revealed an unexpected role of endogenous Homer2 (but not Homer3) in restricting intracellular calcium oscillations coupled to the activity of G protein–coupled receptors (Shin et al. 2003). The idea of a generalized role for constitutive Homers as buffers of calcium signaling has recently been explored (Worley et al. 2007) and is attractive considering the abundance of binding partners involved in calcium signaling pathways. Such a role may exist in addition to a major scaffolding function, and further work is needed to clarify the relative importance of these functions at excitatory synapses.

Human Molecular Genetics Data on Homers

Evidence on the in vivo roles exerted by Homers at the synapse has led to several hypotheses concerning Homer dysfunction in a wide range of neurological disorders (Szumlinski et al. 2006). In particular, the broad spectrum of generic schizophrenia-like behavioral abnormalities exhibited by *Homer1* null mice have made *Homer1* a good candidate for gene-association studies in schizophrenia. One recent study identified numerous single nucleotide polymorphisms (SNPs) in *Homer* genes, including three variants located in exons (Norton et al. 2003). The evidence for association of a single SNP in *Homer1* with schizophrenia was bordering on statistical significance; however, the authors concluded that *Homers* are most likely not implicated in schizophrenia. Similar nominally significant evidence has suggested linkage of *Homer1* gene variants to major depression (Rietschel et al. 2010), treatment response to antipsychotic drugs in schizophrenia (Spellmann et al. 2011), or *Homer2* gene variants to psychostimulant abuse (Dahl et al. 2005). A large multisite study reported no association of *Homer1* or *Homer2* variants with alcohol dependence (Preuss et al. 2010), which failed to substantiate a hypothesized role of Homer2 in alcohol dependence supported by several prior studies in mice. In all, the available evidence linking Homer variants to psychiatric disorders is tenuous, and the weak evidence for association in small-scale human genetics investigations will require further replication and validation to confirm the suspected links.

SAPAP FAMILY

The SAPAP (also called guanylate kinase–associated protein or GKAP) family is composed of four homologous genes encoding

the SAPAP1-4 proteins that are widely yet differentially expressed in the nervous system (Takeuchi et al. 1997, Welch et al. 2004). The SAPAP family was originally identified by a direct interaction with the GK domain of PSD95-family members in yeast two-hybrid screens (Kim et al. 1997, Satoh et al. 1997, Takeuchi et al. 1997). SAPAPs are an abundant component of the PSD (Sheng & Hoogenraad 2007) and interact with a variety of other PSD proteins (Boeckers et al. 1999b, Hirao et al. 2000, Kawabe et al. 1999, Yao et al. 1999), suggesting that SAPAPs are important scaffolding proteins at excitatory synapses.

Mutational Analysis of SAPAP Function In Vivo

SAPAP3 is the only family member strongly expressed in the striatum (Welch et al. 2004), thus offering a unique opportunity to explore the specific function of SAPAP3 at glutamatergic synapses in vivo without potentially confounding effects of functional redundancy arising from other SAPAPs in this brain region. Genetic deletion of *SAPAP3* in mice caused behavioral abnormalities consisting of increased anxiety and compulsive self-grooming to the point of facial hair loss and skin lesions (Welch et al. 2007). These features share similarity with various aspects of core symptoms exhibited by human patients with obsessive-compulsive disorder (OCD), and bare a striking similarity to the phenotypes exhibited by other recently described genetic animal models of OCD-like behaviors (Chen et al. 2010, Shmelkov et al. 2010). Consistent with the localization and predicted function of the SAPAP3 protein, *SAPAP3* null mice also have defects in glutamatergic transmission at cortico-striatal synapses. Remarkably, both synaptic and behavioral defects were rescued by lentivirus-mediated reintroduction of SAPAP3 specifically into the striatum (Welch et al. 2007). This finding establishes the central role of excitatory synaptic dysfunction within cortico-striatal circuitry in the expression of OCD-like behaviors. Additionally, the chronic administration of the selective serotonin reuptake inhibitor (SSRI) fluoxetine successfully alleviated measures of anxiety and compulsive grooming (Welch et al. 2007)—an important distinction given that chronic SSRI treatment is at least partially effective in alleviating symptoms as a first-line treatment in OCD. Thus, the *SAPAP3* null mouse model may serve as a novel tool to identify more effective drugs for the treatment of OCD.

A follow-up study uncovered an altered form of short-term synaptic plasticity expressed at excitatory synapses of striatal medium spiny neurons in acute brain slices from *SAPAP3* null mice (Chen et al. 2011). The mechanism for the anomalous activity-dependent synaptic depression involved a retrograde endocannabinoid signaling pathway through CB1 receptor activation that was engaged under conditions that do not normally activate endocannabinoid signaling in wild-type mice. Further evidence demonstrated the critical involvement of increased group 1 mGluR activity or surface expression as the driving force behind the reduced threshold for engaging endocannabinoid signaling in this experimental paradigm. This study proposes a previously unrecognized role for SAPAP3 in regulating mGluR function in the postsynaptic compartment of excitatory synapses. Further detailed investigation will be required to clarify how this anomalous short-term plasticity at excitatory synapses onto medium spiny neurons in *SAPAP3* null mice may impact synaptic function in vivo and to clarify what implications this has for pinpointing the causal defects underlying compulsive-repetitive behaviors relevant to human OCD. At the synaptic level, the emerging evidence supports the critical involvement of SAPAP3 in controlling both ionotropic (Welch et al. 2007) and metabotropic (Chen et al. 2011) glutamate receptors through a PSD scaffolding role at excitatory synapses.

Human Molecular Genetics Data on SAPAPs

The initial report of OCD-like behaviors in *SAPAP3* null mice has prompted several recent

Paralog: genes that arose by duplication of a gene within the genome; may evolve new functions over the course of evolution

human genetics studies of *SAPAP3* in OCD and obsessive-compulsive spectrum disorders. Zuchner et al. (2009) performed *SAPAP3* gene resequencing analysis in OCD and trichotillomania (TTM), an obsessive-compulsive spectrum disorder, and found an increased frequency of rare nonsynonymous heterozygous *SAPAP3* variants in cases versus controls, thus providing tentative support for a role of *SAPAP3* in OCD and TTM. The majority of the variants represented missense mutations, some of which are predicted to be possibly detrimental to protein function on the basis of bioinformatics analysis. These findings await further validation, including analysis of the functional relevance of these rare *SAPAP3* variants. A second study carried out a relatively large, family-based gene-association study of *SAPAP3* in OCD and grooming disorders (Bienvenu et al. 2009). The preliminary evidence suggests that multiple variations in *SAPAP3* are associated with grooming disorders. No clear association between *SAPAP3* variants and OCD was reported, although grooming disorders without OCD were uncommon in this study, suggesting the possibility that *SAPAP3* variants may be involved in a subtype of OCD involving pathological grooming behaviors. A very recent study of similar design evaluated SAPAP3 as a candidate susceptibility gene in Tourette syndrome, another obsessive-compulsive spectrum disorder, and found a nominally significant association (Crane et al. 2011). A fourth study evaluated SNPs distributed across the SAPAP3 gene to test for association of SAPAP3 variants with TTM and OCD and reported further evidence to link SAPAP3 variants to TTM and early-onset OCD (Boardman et al. 2011). Although the findings of Crane et al. (2011) and Boardman et al. (2011) are represented as supportive of the two earlier studies, these results should be interpreted with caution because statistical correction for multiple testing nullified the nominally significant associations reported in both studies.

Interestingly, in spite of the dearth of evidence on the functional roles of the other SAPAPs, some studies have emerged to suggest involvement of genetic variations in *SAPAP1* and *SAPAP2* in psychiatric disorders. For instance, *SAPAP1* is located in a chromosomal region that was reported to harbor a susceptibility locus for schizophrenia and bipolar disorder (Berrettini et al. 1994, Schwab et al. 1998). This prompted a study to screen for *SAPAP1* mutations in schizophrenia. One SNP was identified in *SAPAP1*, but this SNP was not associated with schizophrenia (Aoyama et al. 2003). In addition, *SAPAP2* was recently identified as one of several novel candidate loci in a large study to search out genome-wide rare CNVs occurring in ASD cases (Pinto et al. 2010). This finding is particularly interesting in light of the demonstrated interaction between SAPAPs and Shank3 (Boeckers et al. 1999b), with strong evidence implicating Shank3 mutations as causative in some ASD cases (Durand et al. 2007, Gauthier et al. 2009, Moessner et al. 2007).

SHANK FAMILY

The SH3 and multiple ankyrin repeat domains (Shank) protein family is coded by three genes (*Shank1-3*) that share a high degree of identity between both paralogs and orthologs. Characterization of this family of genes was initiated by cloning Shank2/CortBP1 (Cortactin binding protein 1) after its identification as a binding partner to Cortactin (Du et al. 1998). Shank1 and Shank3 were subsequently isolated and characterized almost simultaneously by several groups (Boeckers et al. 1999b, Naisbitt et al. 1999, Tu et al. 1999). In the rat brain, the perinatal expression of Shank1-3 is relatively low but rapidly increases during the first weeks of development, peaking at 3–4 weeks (Lim et al. 1999). Expression of Shank1-3 mRNA is prominent in the central nervous system and its protein products are enriched in the PSD (Boeckers et al. 1999a, Lim et al. 1999). Moreover, not only are Shank proteins enriched, they are also some of the earlier elements coalescing at the PSD, predating the arrival of both PSD95 and NMDARs (Boeckers et al. 1999a, Petralia et al. 2005). Finally, the presence of

dendritic-targeting elements in the untranslated regions of Shank1 mRNA adds a further level of complexity toward transcript translocation and regulation in neuronal dendrites and spines (Bockers et al. 2004, Falley et al. 2009).

The Shank protein contains several discrete domains including (from N to C terminal) ankyrin repeat domains, one SH3 domain, one PDZ domain, a proline-rich region, and a sterile alpha motif domain (Han et al. 2006, Lim et al. 1999). This abundance of protein-protein interaction domains enables the interaction of Shank with several other synaptic proteins and suggests an important organizational role for these scaffolding proteins. Specifically, Shanks may sit at a convergent point for three independent subcomplexes within the larger PSD. First, Shank proteins interact with the SAPAP family of proteins (Naisbitt et al. 1999); SAPAP then binds to the PSD95 family of proteins, thereby linking ionotropic glutamate receptors to Shank (Naisbitt et al. 1999). Second, the Homer family of proteins is another important Shank binding partner, linking Shanks to metabotropic glutamate receptors and suggesting that Shank proteins may form a molecular bridge between ionotropic and metabotropic glutamate receptors. Third, Shank proteins interact with several partners involved in the regulation of the actin cytoskeleton, including Cortactin (Du et al. 1998, Naisbitt et al. 1999), α-Fodrin (Bockers et al. 2001), and Abp1 (Qualmann et al. 2004). Finally, recent evidence revealed that Shank and Homer may assemble in a macromolecular platform of interleaving Shank3 dimers and Homer tetramers. Owing to the richness of Shank protein-protein interaction domains and binding partners, it is hypothesized that the Shank-Homer matrix plays a pivotal role in the stabilization and organization of the larger PSD (Baron et al. 2006, Hayashi et al. 2009, Tu et al. 1999).

Mutational Analysis of Shank Function In Vivo

Analysis of *Shank1* expression in the rodent brain reveals that Shank1 is highly expressed in cortical regions and the hippocampal formation (Bockers et al. 2004, Peca et al. 2011). *Shank1* null mice exhibit defects in synaptic function and behavioral abnormalities consistent with deficits in hippocampal function and glutamatergic synaptic signaling (Hung et al. 2008). Local abundance of the Shank-interacting proteins Homer and GKAP was reduced at the PSD in mutant animals. Disruption of *Shank1* also led to smaller dendritic spines in hippocampal neurons and a prevalence of thinner PSDs. Furthermore, perturbation of *Shank1* led to a decrease in synaptic strength and a reduction in the frequency of spontaneous postsynaptic excitatory responses, which could be attributed to the presence of spines lacking functional synapses (Hung et al. 2008). At the behavioral level, *Shank1* null mice display an enhanced acquisition of spatial memories but deficiencies in memory retention in the same test. Contextual memory was perturbed in a test of fear conditioning, whereas conditioned response remained intact—again suggesting hippocampal dysfunction (Hung et al. 2008). These defects in spatial and contextual fear memory are consistent with prominent expression of Shank1 in the hippocampus and the proposed role this protein may exert in synaptic and spine maturation (Bockers et al. 2004, Sala et al. 2001). Recent work has attempted to assess if autistic-like phenotypes could be found in Shank1 null mice. These studies showed that, whereas Shank1 mutants display abnormal motor behaviors and communication impairments, reciprocal social interactions in juvenile animals are not impacted (Silverman et al. 2011, Wohr et al. 2011).

Four different groups have independently generated and virtually simultaneously characterized a total of five Shank3 mutant mouse lines (Bangash et al. 2011, Bozdagi et al. 2010, Peca et al. 2011, Wang et al. 2011). Each line was largely aimed at ablating specific exons in the Shank3 gene to induce genetic lesions and perturb expression of Shank3 isoforms. Interestingly, a remarkable amount of converging evidence on the in vivo function of Shank3 was produced. Most notably, all the lines displayed

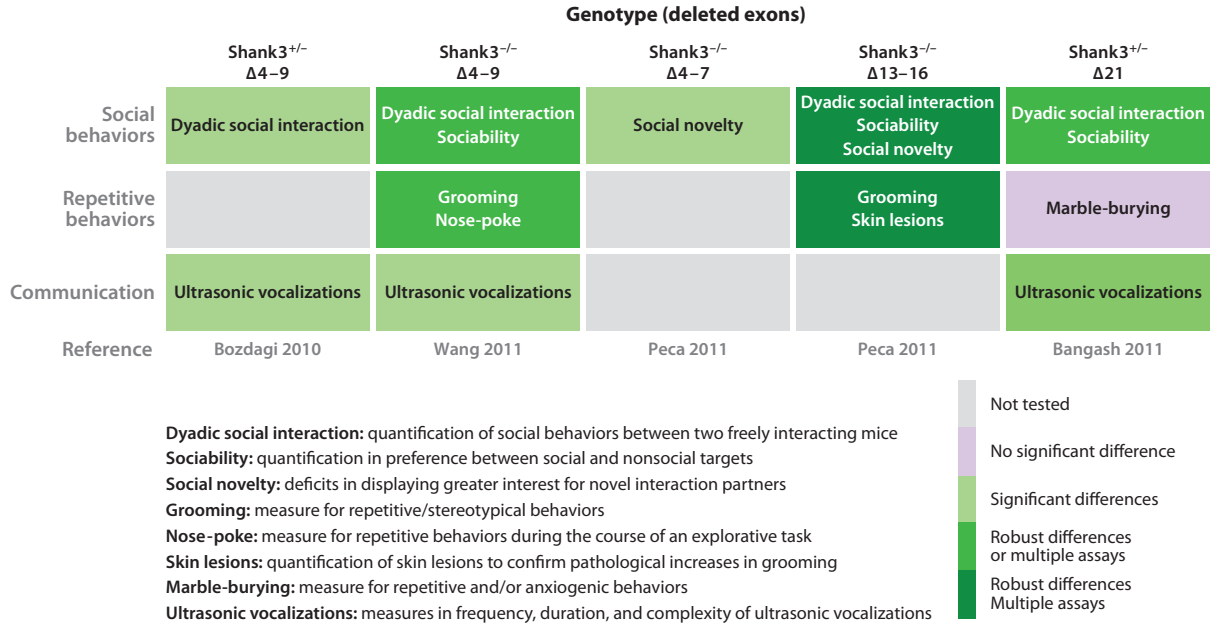

Figure 3

Comparison of autistic-like behavioral deficits in five different Shank3 mutant mouse lines.

varying robustness of several forms of behavioral deficiencies relevant to the study of ASDs, such as deficits in social interaction, abnormal vocalization, and compulsive-repetitive behaviors (**Figure 3**). At the cellular level, *Shank3* mutant mice display a pronounced perturbation in synaptic function, more specifically, a decrease in glutamatergic signaling, loss of synaptic strength, or altered synaptic plasticity (Bangash et al. 2011, Bozdagi et al. 2010, Peca et al. 2011, Wang et al. 2011). From these new studies on *Shank3* mutant mice, one study described a *Shank3* genetic lesion that led to a gain-of-function effect through the expression of a form of Shank3 lacking the C-terminal region (Bangash et al. 2011). This mutant protein promotes the recruitment of endogenous full-length Shank3 isoforms and NMDAR subunits for degradation through the proteosomal pathway. This study offered the first insights into a potential mechanistic role played by a discrete set of *Shank3* mutations relevant to *Shank3* mutations in autism (Bangash et al. 2011, Durand et al. 2007). Interestingly, Shank3 and its close interacting partner SAPAP are established targets for ubiquitination at the PSD in response to changing activity levels (Ehlers 2003, Hung et al. 2010). When taking into account that both Shank3 and SAPAP3 mRNA are among the rare transcripts found in dendrites (Peca et al. 2011, Welch et al. 2004), it is tempting to speculate on the importance of rapid bidirectional control of dendritic translation and synaptic localization of both Shank3 and SAPAP3. Moreover, Shank3 and SAPAP3 are both highly expressed in striatal tissue, and the disruption of either gene leads to defects in cortico-striatal synaptic function; thus, these molecular partners may functionally converge on a common pathway in the brain. Dysfunction of this brain circuitry seems to be crucial in the expression and/or gating of compulsive-repetitive behaviors that represent a core feature of both ASDs and obsessive-compulsive spectrum disorder (Peca et al. 2011, Welch et al. 2007).

Human Molecular Genetics Data on Shanks

Phelan-McDermid syndrome (PMS) is a genetic condition characterized in part by

delayed or absence of speech and language and a high incidence of autistic behaviors in afflicted children (Phelan et al. 2001). A genetic lesion in the terminal region of human chromosome 22 has been identified in PMS, and in most 22q13 microdeletions a large number of genes, including *Shank3*, are ablated. However, from the multiple genes disrupted in PMS patients, only *Shank3* has been strongly associated with the major neurological complications arising from 22q13 chromosomal aberrations (Bonaglia et al. 2011, Delahaye et al. 2009, Wilson et al. 2003). Also in support of this view, minimal deletions in 22q13.33 that still affect *Shank3* promote the full range of PMS symptomatology, whereas ring chromosome aberrations or 22q13.33 microdeletions that leave *Shank3* intact do not (Jeffries et al. 2005, Misceo et al. 2011). Importantly, mutations in Shank3, including microdeletions, nonsense mutations, and recurrent break points, are found in ASD patients diagnosed outside of PMS, thereby strongly suggesting that a monogenic form of ASDs can be triggered by perturbing this postsynaptic protein (Durand et al. 2007, Gauthier et al. 2009, Moessner et al. 2007). Finally, Shank3 has also been linked with a potential role in the development of schizophrenia (Gauthier et al. 2010).

More recently, CNVs have been proposed to account for a substantial percentage of genetic lesions in nonsyndromic ASD cases (Beaudet 2007, Sebat et al. 2007). CNVs affecting *Shank2* and *SAPAP2* have also been identified in patients affected with ASDs or mental retardation, again suggesting a role for these families of genes in psychiatric disorders (Berkel et al. 2010, Pinto et al. 2010).

SUMMARY

Deciphering Structural and Functional Roles of Postsynaptic Scaffolding Proteins at the Synapse

The recent findings we highlight stress the dynamic and evolving view of the PSD, with emphasis here on the roles of the postsynaptic scaffolding proteins in this specialized structure. By harnessing a multitude of biochemical, molecular, electrophysiological, and behavioral methodologies, researchers in this field are methodically unraveling the precise functions subserved by individual scaffolding proteins. The application of mouse genetic engineering in recent years has especially facilitated major advancements in our knowledge of the in vivo functions carried out by the major scaffolding protein families through analysis of both loss-of-function and gain-of-function mutations. These mutant mice have collectively provided convincing confirmation of physiological functions previously demonstrated only in vitro and have led to new discoveries that have allowed us to refine and/or reinterpret the existing models (e.g., defining the functional redundancy among PSD95 family proteins; uncovering a putative calcium buffering role of Homers in neuronal and non-neuronal tissue). Despite the overt complexity of the postsynaptic compartment at excitatory synapses, the once seemingly insurmountable task of a complete molecular-genetic functional dissection of the major PSD components is emphatically feasible.

Integration of Human and Mouse Genetics to Elucidate Gene Function in Health and Disease

It has sparked great interest that a growing number of genetically modified mice harboring mutations in distinct postsynaptic scaffolding proteins exhibit behavioral phenotypes that are reminiscent of specific human psychiatric disorders. In some instances the discoveries were fortuitous, whereas in other cases the mutant mice were created with foreknowledge of the gene having been implicated in disease susceptibility or causality. Although no animal model can fully recapitulate all the core features of a particular complex human psychiatric disorder, each animal model may express a subset of core features that is easily quantifiable and amenable to detailed mechanistic investigation at a level that is not possible in humans. Thus, detailed multilevel analysis of the functional

consequences of gene mutations in animal models is indispensable for searching out gene function in both health and disease, as exemplified here by the work concerning the in vivo functional roles of postsynaptic scaffolding proteins.

In considering the recent work on *SAPAP3* null mice and *Shank3* mutant mice, the proposed relevance of the mutant mouse phenotypes to a human disorder has been strengthened by complementary human genetics data linking variations in the gene (or regions harboring the gene of interest) to the same disorder or related disorders in humans (e.g., *SAPAP3* and obsessive-compulsive spectrum disorders, *Shank3* and autism-spectrum disorders). Although such findings can be viewed as strongly supportive, it is crucial to point out that evidence from human genetics studies supporting the association of a particular gene variation with a human psychiatric disorder does not establish causality of that gene, but instead establishes the overrepresentation of that particular gene variation with the diseased state. Genetic-association studies in psychiatric disorders leave open the mechanism(s) by which specific genetic variations perturb gene function and the impact of these alterations on neuronal and brain circuitry function. As a concluding note, it is valuable to expand the view beyond the relatively narrow scope of postsynaptic scaffolding proteins, as a flurry of recent human genetics studies have implicated a broad spectrum of genes related to synaptic function as contributing to susceptibility in human mental health disorders (Gilman et al. 2011, Gratacos et al. 2009, Hamdan et al. 2011, Piton et al. 2011, Voineagu et al. 2011). Deciphering causal genetic variants will undoubtedly be a monumental task that will keep our attention firmly focused on the remarkable structural and functional complexity of the synapse.

FUTURE ISSUES

1. Human genetics studies are identifying disease-linked genetic variants at an overwhelming pace. Defining which genetic variants are benign and which are pathological represents a major goal in translational neuroscience.
2. Engineering genetically modified mice with disease-relevant mutations will greatly facilitate this effort.
3. In creating new genetic mouse models, researchers should consider a variety of strategies, including but not limited to the following: null alleles, knock-in alleles, alleles with specific gene CNVs, and chromosomal aberrations. The most appropriate design will depend on the unique goals of each study.
4. Delineating cell-type-specific functions of PSD scaffolding proteins in vivo using molecular genetics tools will be of exceptional value to dissecting the circuitry basis of behavior.

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