Regulation and Function of Activity-Dependent Homer in Synaptic Plasticity

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Abstract
Alterations in synaptic signaling and plasticity occur during the refinement of neural circuits over the course of development and the adult processes of learning and memory. Synaptic plasticity requires the rearrangement of protein complexes in the postsynaptic density (PSD), trafficking of receptors and ion channels and the synthesis of new proteins. Activity-induced short Homer proteins, Homer1a and Ania-3, are recruited to active excitatory synapses, where they act as dominant negative regulators of constitutively expressed, longer Homer isoforms. The expression of Homer1a and Ania-3 initiates critical processes of PSD remodeling, the modulation of glutamate receptor-mediated functions, and the regulation of calcium signaling. Together, available data support the view that Homer1a and Ania-3 are responsible for the selective, transient destabilization of postsynaptic signaling complexes to facilitate plasticity of the excitatory synapse. The interruption of activity-dependent Homer proteins disrupts disease-relevant processes and leads to memory impairments, reflecting their likely contribution to neurological disorders.

Introduction
The postsynaptic density (PSD) is an architecture of specialized proteins responsible for mediating the response to converging synaptic input. Rearrangement of PSD proteins, as a consequence of changes to the pattern of neurotransmission, leads to alterations in synaptic strength, required for learning and memory [1–3]. Hence, the study of PSD protein dynamics represents a fundamental route toward understanding synaptic plasticity and may be central to discerning the etiologies of neuropsychiatric disorders such as schizophrenia [4]; strongly supported by recent genomic studies in human patients [5].

The family of Homer scaffolding proteins (Homer1–3) are evolutionarily conserved [6] key components of the PSD and form links between receptors, ion channels, and other scaffolding proteins [6, 7]. They function to mediate the assembly of multiprotein complexes in intracellular microdomains. Homers share an N-terminal ligand-binding domain, which interacts with the proline-rich sequences contained within PSD proteins involved in regulating synaptic architecture, intracellular calcium...
signaling, and neuronal development. The majority of Homer transcript variants, generated via alternative mRNA splicing, are long, constitutively expressed and encoded by Homer1b, Homer2a and b, Homer3a and b. However, 2 truncated forms of Homer1, known as Homer1a and Ania-3, are shorter, activity-induced immediate early genes [8]. These short Homer1 isoforms possess a common enabled/vasodilator-stimulated phosphoprotein homology 1 (EVH1) domain but lack a coiled-coil (CC) domain that permits longer Homer proteins to oligomerize with one another [9]. As a consequence, Homer1a and Ania-3 bind as dominant negative regulators, allowing them to disrupt interactions between long, constitutively-expressed Homers and their effector proteins [6, 10]. The unique C-terminal sequence of Homer1a is well conserved across mouse, rat, and human species suggestive of evolutionally conserved function, although the C-terminus of the Ania-3 transcript, found in rodents, is not conserved across these mammalian species [6, 11, 12].

Homer IEGs appear to be powerful modulators of synaptic plasticity and are the subject of the review. The literature surrounding Homer1 IEGs indicates that their precise temporospatial expression and recruitment to active synapses is essential for the regulation of PSD protein complexes and calcium signaling in dendritic spines and may therefore be important for learning and memory [13–16]. We discuss potential mechanisms through which Homer1 IEGs may mediate synaptic plasticity. Most research to date has focused on the function of either the well-conserved Homer1a transcript or short Homer1 isoforms as a collective in rodents, so the distinct roles of activity-dependent Homer1a and Ania-3 remain unknown (although see below and Clifton et al. [16]). Therefore, the majority of this review focuses on Homer1a function.

Protein Structure and Interactions

Homer proteins contain a highly conserved EVH1-like domain [17, 18], which maintains much sequence homology with other vasodilator-stimulated phosphoprotein proteins responsible for regulating cytoskeletal dynamics [19]. A neighboring proline motif is specific to the Homer1 subfamily [18]. Through the EVH1 domain, Homer proteins interact with proline-rich sequences of a range of targets including group 1 metabotropic glutamate receptors (mGluR1 and mGluR5), inositol 1,4,5-triphosphate receptors (IP3Rs), Shank scaffolding proteins, ryanodine receptors, transient receptor potential canonical (TRPC) channels, voltage-gated calcium channels, and dynamin 3 [6, 9, 20–26]. Long Homer isoforms, which form multimers through their (low homology) carboxy-terminal CC domains, mediate functional links between these PSD proteins, facilitating signal transduction [6, 27, 28].

The expression of shorter Homer1 isoforms occurs through alternative splicing, whereby the premature termination of transcription downstream of exon 5 creates the truncated Homer1a and Ania-3 proteins (Fig. 1) [7, 11, 29]. The fifth intron of the Homer1 gene comprises sections of DNA specific to the transcription of Homer1a or Ania-3 mRNA [11]. These isoforms lack a C terminal CC domain and leucine zipper motifs, and the absence of the CC domain prevents Homer1a and Ania-3 from
forming homo- or hetero-oligomers. Hence, since their discovery [7, 12], Homer1a and Ania-3 are widely regarded as dominant negative regulators of long Homer function, uncoupling them from effector proteins through competition for the proline-rich sequence of the target protein [8, 17]. Indeed, Homer1a protein blocks the binding of long Homers to group I mGluR and disrupts long Homer-mGluR-mediated functions [6, 20, 30].

Short Homer proteins are synthesized in the soma before vesicular transportation to dendrites [7, 14] through interactions with Group I mGluRs [27, 31]. Long Homer1 isoforms are also transported with group I mGluRs to dendrites [31, 32]; yet, in the absence of Homer1a, retain the receptor complex within endoplasmic reticulum (ER), inhibiting the surface expression of mGluR5 [31–34]. The induction of Homer1a protein through neuronal excitation then interrupts the endoplasmic retention of mGluR5, permitting their trafficking to the membrane [34]. Hence, long Homers retain a pool of group I mGluRs at the ER until released by activity-induced short Homers (Fig. 2), again demonstrating the antagonistic effects of long and short Homer isoforms.

Homer1 IEG Induction and Regulation

Neuronal activity-induced expression of short Homer1 mRNA has been observed throughout brain structures known to be involved in learning and memory, including the cerebral cortex, hippocampal CA1, CA2, CA3, and dentate gyrus, striatum, and amygdala [6, 7, 16, 35–41]. The induction of Homer1a has been extensively investigated in vitro including neuronal depolarization with ionotropic glutamate receptor agonists, N-methyl-D-aspartate (NMDA), kainite, and potassium channel blockers [31], application of brain-derived neurotrophic factor (BDNF) [42], traumatic injury [43, 44], and evoking epileptiform activity with bicuculline and 4-aminopyridine [45]. Meanwhile the induction of Homer1a in
vivo has been reported following electroconvulsive shock [6, 7, 11, 46], long-term potentiation (LTP) [27, 46], exposure to psychoactive drugs such as cocaine [7, 40], lysergic acid diethylamide [47, 48], and NMDA receptor antagonist ketamine [49, 50], direct dopamine D1 receptor stimulation [12], typical and atypical antipsychotic administration [36, 37, 51, 52], Pavlovian fear conditioning [16, 42], instrumental learning [53], exploration of a novel environment [16, 38, 54], running [55], visual experience [7], environmental stressors [39, 56], and neuropathic pain [57]. Importantly, it is exclusively the short, IEG isoforms of the Homer1 gene that are induced under these conditions, while the expression of the longer isoforms typically remains unchanged.

Neuronal activation induces a switch in the transcription of the Homer1 gene to the preferential expression of short isoforms. This switch is created through an activity-dependent change in the polyadenylation site usage, altering transcription termination, and is controlled by myocyte enhancer factor 2 transcription factors [11, 58, 59]. With an aim to gain further insight into the activity-dependent regulation of Homer1a transcription that may regulate synaptic plasticity during memory consolidation, Mahan et al. [42] examined the epigenetic modulation of the Homer1a gene during BDNF-induced plasticity in vitro and BDNF-dependent learning in vivo. BDNF prompted an upregulation of Homer1a in primary amygdala and hippocampal cultures that was dependent upon MEK and ERK signaling mechanisms. Around the Homer1 promoter region, they observed an increase in histone H3 acetylation, a marker of enhanced gene transcription, in hippocampal primary cell cultures and a decrease in histone H3K9 methylation, a transcriptional repressive marker, in amygdalar cultures. When mice underwent Pavlovian fear conditioning, the consolidation of which involves BDNF signaling [60–62], the same Homer1 epigenetic modifications that were seen in vitro were found in mouse hippocampal and amygdalar tissue [42]. This work demonstrates 2 possible regionally defined epigenetic mechanisms through which activity-induced Homer1 transcripts may be generated during processes of learning and memory and developmental synaptic maturation to bring about the necessary plastic changes at the synapse.

Homer1a expression is developmentally regulated. Homer1a is in a prime position to impinge on synaptogenesis and synaptic pruning mechanisms during brain maturation given (i) its functional location at the glutamate PSD, (ii) its interactions with NMDA receptor complexes, (iii), the critical requirement of glutamate synaps-es in the refinement of neuronal connections during development [63–67], and (iv) the developmental impairments caused by disrupting glutamate receptor complexes [68, 69]. Postnatal forebrain expression of Homer1a increases from birth, peaking between 3 and 5 weeks [7]. Montes-Rodríguez et al. [41] demonstrated that induction of Homer1a by neuronal activity was related to postnatal age. Maximal electroconvulsive shock treatment in rats only increased hippocampal Homer1a expression when applied in the second postnatal week (but not the first), which corresponds to the maturation of glutamatergic transmission required for synaptic plasticity. The quantity of hippocampal activity-induced Homer1a induced by maximal electroconvulsive shock (measured by intra-nuclear foci intensity) peaked when applied at 3 weeks of age, in parallel with synaptic maturation, suggesting a role in the refinement of neuronal circuits [41, 70]. The balance of short to long Homer1 isoforms is also an important regulator of axonal path finding in developing neurons [71] and unsurprisingly, altered Homer1a expression causes developmental impairments in locomotor activity, motor coordination, and motor learning [72–74].

**Regulation of mGluR-NMDA Complexes**

At the PSD, short Homer1 proteins act to interrupt the polymeric matrix formed by interactions of long Homer1 isoforms with other components [6, 27, 28]. In cultured hippocampal neurons, overexpression of Homer1a, or its induction by BDNF, prompts a reduction in long Homer1c clusters without decreasing the amount of protein [75]. Clusters of F-actin and PSD-95 are similarly reduced, through disruption of their association with the scaffolding protein Shank [9, 75, 76], and dendritic spine size is decreased [76]. Hence, by prompting the movement of PSD proteins away from the synapse, Homer1a appears to redistribute the synaptic architecture constructed by long Homer1 proteins in response to neuronal activity. In this way, Homer1a brings about reorganization of PSD scaffolds and processes of spine morphogenesis that are both critical for synaptic plasticity [77, 78].

The interaction between Homer and group I mGluRs (mGluR1 and mGluR5) has been a particular focus of functional studies because of the role of Homer plays as an intermediary between mGluRs and other effector proteins, including the NMDA receptor [20, 79, 80]. Reciprocal signal transduction between group I mGluRs and NMDA receptors permits the regulation of NMDA-
evoked currents by mGluR activation [79–82] required for a range of NMDA-dependent processes [83, 84]. However, the directionality of NMDA and group I mGluRs modulation varies between studies. While some studies report that group I mGluR activation augments NMDA activity [80–82], others report inhibition [2, 79, 85]. The emerging explanation for these opposing outcomes is that they depend upon the differential involvement of long and short Homer1 proteins.

NMDA receptors are located within the PSD, whereas group I mGluRs are typically located at extrasynaptic and perisynaptic regions [86, 87] and thus do not colocalize with NMDA receptors [2]. Interactions between the 2 glutamate receptors are mediated by a Homer-Shank-GKAP-PSD95 scaffold [21, 88]. It has been suggested that mGluRs use long Homer-containing scaffold to facilitate NMDA activity, supported by the observation that the potentiation of NMDA receptor currents by group I mGluR agonists is blocked by postsynaptic transfection of Homer1a [80]. Other studies have demonstrated a Homer1a-dependent inhibition of NMDA receptor activity that is calcium-independent [79] and requires the integrity of the EVH1 domain of Homer1a [76], highlighting the functional importance of direct mGluR–Homer interactions.

This model does not yet fully explain how group I mGluRs promote the inhibition of NMDA currents in the presence of Homer1a reported by studies using sustained stimulation paradigms [2, 79]. Recent evidence shows that mGluR1a-mediated Homer1a-dependent inhibition of NMDA receptors gives rise to the coimmunoprecipitation of the β subunit-containing G-protein with NMDA NR1 subunits, which is attenuated by disrupting G-proteins pharmacologically [79]. Similar results could be achieved by transfecting neurons with Shank3 mutants that are unable to bind Homer complexes, but not by mutants unable to bind the GKAP-PSD95 complex [79]. These data indicate that Homer1a releases group I mGluRs from their perisynaptic attachment to the scaffolding complex, permitting their translocation into the PSD and the subsequent physical inhibition of NMDA receptors via G protein (containing βγ subunits). This notion is supported by a bioluminescence resonance energy transfer study of cultured hippocampal neurons, which imaged spine-specific protein–protein interactions between mGluR5a and NMDA receptors only in the presence of Homer 1a, prompting an inhibition of NMDA currents [2]. Hence, group I mGluRs regulate NMDA receptor activity. Whether that regulation is facilitatory or inhibitory is determined by the mutually exclusive interaction with long or short Homer proteins, respectively. Homer1a-induced scaffold remodeling may therefore represent a switch for mGluR-NMDA receptor function upon synaptic stimulation that could be important for the initiation of plasticity processes such as LTP and long-term depression (LTD).

Calcium Signaling

The majority of the proteins that Homer is known to interact with are involved in calcium homeostasis, including mGluRs, IP3Rs, TRPC channels, ryanodine receptors, and voltage-dependent calcium channels (VDCCs), particularly L-type VDCC. Elevation in intracellular calcium in dendritic spines modifies neuronal excitability, initiates signaling cascades, and recruits new membrane proteins, ultimately adjusting synaptic strength [89–91].

It has long been recognized that group I mGluRs regulate the activity of the calcium-releasing IP3Rs on intracellular ER stores via Homer and Shank protein scaffolds [20, 92–94]. In neocortex pyramidal neurons, intracellular injection of Homer1a protein dose-dependently enhanced spike-induced calcium influx through VDCC and lowered the threshold for calcium spikes [95]. The same is not achieved by injection of long Homer1b/c. Induction but not the maintenance of the augmented calcium signal with synaptic activity was dependent on mGluR-IP3R signaling pathways. Thus, via interactions with mGluR and IP3R, Homer1a can enhance neuronal excitability maintained by the upregulation of VDCC currents.

Homer1a may also participate directly in the upregulation of neuronal VDCCs. Indeed, L-type VDCC subunits, CaV1.2 and CaV1.3, possess Homer-binding domains on their carboxyl termini [26, 96]. A study of excitation–contraction coupling, which modeled calcium-induced calcium release by ryanodine receptor 2 (RyR2) and CaV1.2 in human embryonic kidney cells, suggests that the communication between CaV1.2 at the cell surface and RyR2 on ER is mediated through the Homer–calcium channel interaction [96]. Long Homer1b/c facilitates an interaction between RyR2 and CaV1.2, which decreases the sensitivity of the cell to membrane depolarization-induced calcium elevations, whereas Homer1a disassembles the interaction, increasing the sensitivity and efficiency of calcium-induced calcium release [96] (Fig. 3). These observations corroborate closely with those from neocortex pyramidal neurons [95], both illustrating how activity-
induced Homer isoforms permit a rise in intracellular calcium concentration. In astrocytes, however, the interruption of Homer1b/c-mediated mGluR5-ER interactions by Homer1a leads to a decrease in calcium signaling and glutamate release [97].

The link between ryanodine receptors and L-type voltage-gated calcium channels is not the only occurrence of Homer1 facilitating the signal transduction between ER and cell plasma membrane proteins mediating calcium signaling. IP3Rs communicate with TRPC family cation channels within a complex assembled by Homer1 [25]. Similarly to the regulation of L-type calcium channels, the disassembly of this complex increases TRPC channel activity and calcium influx important for store-operated calcium entry [25]. TRPC-Homer1-IP3R disassembly is regulated by IP3 binding and ER calcium store depletion [25, 98, 99], although expression of Homer1a similarly causes complex dissociation by interrupting the coupling between long Homer isoforms and TRPC, permitting channel opening by the calcium sensing stromal interacting molecule 1 [25, 99, 100]. Homer1a has also been reported to translocate TRPC complexes to the membrane, where they are spontaneously active [98].

These studies collectively demonstrate that activity-induced Homer proteins dynamically regulate the communication between calcium signaling proteins to achieve the facilitation of calcium currents in neurons. Calcium elevations through NMDA and mGluR-coupled signaling cascades are important components of spike-timing-dependent synaptic plasticity and determinants of the directionality of changes in synaptic strength [101, 102]. Therefore, the role of Homer1a in initiating calcium entry is highlighted as a key modulator of synaptic plasticity.

**Functional Plasticity**

We have discussed that Homer1a is regulated by neuronal activity and interacts with key components of the PSD that mediate synaptic plasticity; we now present the evidence that short Homers are themselves functionally involved in synaptic plasticity. This work implicates Homer1a and Ania-3 in the local regulation of...
synaptic strength and the global scaling of synaptic excitability.

Synaptic strength may be modified by the trafficking and phosphorylation of AMPA-type glutamate receptors in the postsynaptic membrane, causing an adjustment of excitatory postsynaptic currents [103, 104]. This process is in part driven by group I mGluR activation [105, 106]. Overexpression of Homer1a in hippocampal neurons can globally decrease surface AMPA receptors [15, 76, 107], reduce GluA2 subunit tyrosine phosphorylation [15], and block the maintenance of LTP [107, 108]. These effects are dependent on group I mGluR signaling, yet do not require the binding of glutamate to the receptors [15]. Since Homer1a has been shown to activate group I mGluRs independently of glutamate [15, 109], this suggests a role for Homer1a in these glutamate-independent cellular mechanisms downregulating synaptic strength. In concordance, knocking out either the Homer1 gene or the short Homer1 isoforms results in an upregulation of postsynaptic AMPA receptors and currents [15, 107]. In contrast, one study reported an increase in synaptic AMPA receptors following Homer1a overexpression [110], which may reflect differences in experimental protocols, but supports the notion that Homer1a-associated scaffold remodeling can lead to the scaling up or down of synapses. Indeed, Van Keuren-Jensen and Cline [111] demonstrated in tadpole optic tectal neurons that the application of group I mGluR agonists to cells with a low Homer1a/Homer1b ratio increased AMPA currents, similar to cells that had been removed from tadpoles after >12 h of darkness. Conversely, either the exogenous expression of Homer1a or Homer1a induction through visual stimulation for >4 h reversed the mGluR-mediated change in AMPA currents. These studies clearly demonstrate the involvement of Homer1a in AMPA receptor trafficking and the homeostatic scaling of synaptic strength.

The role of Homer1a in homeostatic synaptic scaling extends to the regulation of AMPA receptors during sleep [112–114]. A recent study showed that the removal of AMPA receptors in mouse forebrain during sleep depends on the disruption of group I mGluR signaling scaffolds by Homer1a [112]. It is proposed that this mechanism of homeostatic scaling is coordinated by circadian patterns of noradrenaline and adenosine during the accumulation of sleep need, and which promotes synaptic remodeling for the facilitation of memory consolidation [112].

The mechanism through which Homers regulate mGluR-mediated AMPA plasticity may involve their coupling to dynamin 3 in endocytic zones [24]. Long Homers physically tether clathrin-positive endocytic zones near the PSD through interactions with Shank and dynamin 3, to permit local cycling and recapture of AMPA receptors [24, 40]. Disruption of this link by the expression of Homer1a in hippocampal neurons uncouples the endocytic zones from the PSD, which leads to a decrease in the number of postsynaptic membrane AMPA receptors [115]. Therefore, Homer1a induction can remove the AMPA cycling capacity of dendritic spines regulating synaptic strengthening. Further work has examined the recruitment of Homer1a to active synapses. Okada et al. [14] demonstrated that soma-derived Homer1a was rapidly recruited from dendrites specifically into activated spines. This only occurred if NMDA receptors were stimulated and required extracellular calcium and the nitric oxide-protein kinase G signaling pathway. Trapping of Homer1a into spines did not, however, require group I mGluR activation. The recruitment of Homer1a may therefore represent a synaptig tag for recent activity for subsequent spine remodeling and late phase synaptic plasticity mechanisms, including the targeting of de novo plasticity-related proteins, which are required for the input selective stabilization of changes required for information storage [116].

**Learning and Memory**

The long-term maintenance of synaptic strength for memory consolidation requires de novo protein synthesis and scaffold remodeling over an extended period of time following an initial synaptic event [60, 117]. One of the intriguing aspects of Homer1a function is its expression following neuronal activity, which occurs in conjunction with the expression of Arc, another IEG critical for the regulation of synaptic plasticity and memory consolidation [38, 118, 119]. Recent work by our group shows that both forms of activity-dependent Homer1, Homer1a and Ania-3, are induced across CA1, CA3, and dentate gyrus hippocampal subfields during associative fear learning in rats, with more prolonged expression of Homer1a compared with Ania-3, particularly within the CA1 subregion [16]. A variant of the associative learning task (known as the Context Pre-exposure Facilitation Effect) allowed us to precisely measure the associative learning component and revealed induction of both Homer1a and Ania-3, but in the CA1 only. Meanwhile, during exploration of a novel environment, Homer1a,
Ania-3, and Arc are induced in hippocampal neurons [16, 38, 54], implying that their coordinated activity may be necessary for forming a memory pertaining to that environment.

Our recent work also sought to measure the expression of both short Homer isoforms in the recall of associative contextual fear memory, as well as the extinction of memory through longer reexposure to the context in rats. We found that recall of memory induced both Homer1a and Ania-3, across all hippocampal subfields, although Ania-3 had a more curtailed profile. Similarly, we found Homer1a and Ania-3 to be broadly increased across each hippocampal subfield following memory extinction, with Ania-3 expression again being more transient [16]. These isoforms are predicted, therefore, to be involved in retrieval-related memory mechanisms and suggests differential function and/or regulation of the 2 activity-dependent isoforms.

Other studies have evaluated the effect of manipulating the expression of short Homer isoforms on learning and memory. Homer1a null mutant mice display a mild deficit in contextual fear memory consolidation and retention, but not with repeated reinforcement [120]. Further, a brief unreinforced retrieval trial resulted in a weakened contextual fear memory. This may be an indication of impairment in reconsolidation, but it could also indicate weaker learning that is more susceptible to extinction. The study indicated that extinction per se was intact. Similar results in Homer1a KO mice have been reported for cued fear conditioning, which show weaker and less stable fear memory [42]. The study indicated attenuation epigenetic changes – increased H3 acetylation and decreased H3K9 methylation of the Homer1 promoter – which were dependent on BDNF in wildtypes; changes that were rescued by the histone deacetylase inhibitor sodium butyrate. This is consistent with sodium butyrate strengthening fear conditioning [121]. Reduced gene dosage had no effect on sensory processing or anxiety [120, 122]. Thus, together these results suggest that Homer1a regulates the strength of learning through enhancing consolidation.

A recent study using both homo- and heterozygote Homer1a genetic models showed similar consolidation deficits in mice trained in a spatial version of the water maze, with deficits seen in memory retention during long-term probe trials [122]. Homer1 knockout mice show the same behavioral phenotype, but overexpression of Homer1a via AAV-mediated transfer was not able to restore performance [123]. Furthermore, the observations that overexpression of Homer1a in the hippocampus does not affect long-term reference memory acquisition or retention [108, 124] suggest a lack of direct effect of hippocampal Homer1a on long-term associative memory in models that are not confounded by compensatory developmental changes associated with germline/global manipulations of Homer1a expression. However, Homer1a overexpression in the adult hippocampus impaired short-term working memory and may influence performance strategy in these more instrumental tasks of long-term memory [108, 124]. The role for both Homer1a and Ania3 on encoding and retrieval-mediated memory processes remains to be fully understood and needs to consider the contribution across the network supporting memory processing in different behavioral tasks. Indeed, unlike the hippocampus, overexpression of Homer1a in the adult amygdala results in impairments in fear conditioning [125], suggesting that high and low levels of Homer1a impair learning when these occur in different brain regions, that may reflect the underlying differences in the way the amygdala and hippocampus support fear learning [126, 127].

**Implications for Psychiatric Disorders**

Multiple genomic studies in patients have revealed associations between single-nucleotide polymorphisms in the human HOMER1 gene with a variety of psychiatric disorders including schizophrenia [128, 129], autism spectrum disorder [130], major depressive disorder [131], suicide attempt [132, 133], cocaine dependence [134], and opiate abuse [135], although these genetic associations are not conclusive, requiring further replication. Meanwhile, functional studies in rodents point toward a major role for Homer1a in pathological processes related to neuropsychiatric disorders [122, 136] and antidepressant action [137, 138], including its induction in limbic-corticostriatal circuits; the same circuits responsible for mediating cognitive and emotional functions in humans [139]. Here, we provide an overview of mostly preclinical evidence implicating Homer1a in neuropsychiatric disorders including fragile X syndrome, autism spectrum disorder, and schizophrenia.

**Fragile X Syndrome and Autism Spectrum Disorder**

Perhaps the strongest evidence for the involvement of Homer IEGs in neurological disorders derives from studies of Fragile X mental retardation protein (FMRP; Fig. 4). The absence of expression of FMRP (coded by the FMR1 gene) causes fragile X syndrome, a neurodevelop-
mental disorder with a wide range of characteristic neurological, neuropsychiatric, and cognitive deficits [140, 141]. FMRP deletion is also the most common single-gene cause of autism spectrum disorder, while its binding partner (CYFIP1) and downstream targets are implicated in schizophrenia and major depressive disorder [142–146]. FMRP is a negative regulator of group I mGluR-dependent protein synthesis [147], and mice lacking Fmr1 show enhanced long-term mGluR-mediated LTD of postsynaptic AMPA currents [148]. It was demonstrated that stable mGluR5-mediated translation initiation and LTD are dependent on mGluR5 – long Homer interactions [149, 150], which are diminished in Fmr1 knockout mice [151]. Instead, there is increased association between mGluR5 and Homer1a in mice lacking Fmr1, leading to agonist-independent activation of mGluR5 [109, 150, 151]. Ronesi et al. [150] generated an Fmr1/Homer1a (and Ania-3) double knockout in an attempt to normalize mGluR5 function. The additional deletion of the short Homer1 isoforms restored mGluR5–long Homer interactions, stabilized translation rates, and reversed fragile X syndrome-relevant behavioral phenotypes. The abnormal translational control of specific FMRP target mRNAs or altered mGluR-mediated LTD in Fmr1-knockout mice was not rescued by Homer1a deletion, however, [150].

In more recent work, the consequences of disrupted mGluR5–long Homer interactions were assessed in a new, second-generation Fmr1 KO mouse model with total absence of detectable Fmr1 transcripts [152, 153]. In this genetic model, mGluR5 was found to be more mobile at hippocampal synapses, resulting in increased clustering of mGluR5 with NMDA receptors. As a result, Fmr1 KO mice displayed a decrease in NMDA current amplitude, and mGluR-mediated LTD of postsynaptic NMDA currents was absent in the CA1 of Fmr1 KO mice. Deficits in hippocampal-dependent memory and NMDA receptor function/plasticity were rescued by specific knockdown of Homer1a in the CA1 of Fmr1 KO mice [152]. Together, these studies suggest that a higher ratio of short/long Homer proteins interacting with mGluR5 is responsible for disrupting mGluR5-mediated signaling in fragile X syndrome, contributing to the disorder. The proposed therapeutic action provided
by mGluR5 antagonists in Fragile X syndrome [154] may be due to inhibition of Homer1a/mGluR5-mediated events.

**Schizophrenia**

mGluR5 signaling complexes are also a potential target for therapy in schizophrenia [155]. Critically, Homer1a and Ania-3 induction is manipulated by environmental stimuli that impact on the manifestation of psychosis (reviewed in Szumlinski and Kippin [156]). For example, acute cocaine administration in rodents induces a pronounced elevation of Homer1a expression in the striatum, prefrontal cortex, and ventral tegmental area [7, 40, 157]. This response is necessary for the regulation of cocaine sensitivity [123, 158]. Psychotomimetic NMDA receptor antagonists such as ketamine and MK-801 are thought to model some aspects of schizophrenia pathology and induce Homer1a expression [49, 50], while antipsychotics such as haloperidol and clozapine also modulate Homer1a [36, 37, 52, 159, 160] and Ania-3 expression [160].

Furthermore, the ratio of short-to-long Homer1 protein may be abnormal in patients with schizophrenia. In analyses of protein expression in post-mortem hippocampus, Matosin et al. [161] showed that there was increased HOMER1A, but decreased long isoforms HOMER1B/C, in the CA1 region of patients compared to controls. Similarly, HOMER1A was increased in interneurons of the hippocampal stratum oriens of schizophrenia patients, although HOMER1A was also increased in patients with other neuropsychiatric disorders [136]. These findings are consistent with decreased pan-HOMER1 protein in the hippocampus and prefrontal cortex of patients with schizophrenia [162] and behavioral preclinical phenotypes observed in Homer1 whole-gene knockout mice that may model aspects of schizophrenia (impaired pre-pulse inhibition, increased anxiety, and enhanced locomotion in response to MK-801 or methamphetamine) [72]. In sum, these studies imply that the imbalance between the competitive short/long Homer1 isoforms contribute to the expression of schizophrenic symptoms in humans.

**Conclusions**

Short-form Homer1a is recruited to active dendritic spines upon stimulation and de novo Homer1a protein is synthesized somatically and transported to the PSD, thereby facilitating short- and long-term scaffold remodeling for early and late phases of synaptic plasticity. Primarily, its function is the dominant negative disruption of functional synaptic architecture constructed by long Homer1 proteins, which can result in a switch of group I mGluR function, receptor translocation, or the accommodation of calcium entry. These findings suggest that the role of short Homer proteins is to transiently destabilize the PSD in order to permit scaling of the most currently or recently active synapses; or in other words, to selectively facilitate the plasticity of excitatory synapses to support critical processes such learning and memory. Meanwhile, the disruption of the human orthologue, HOMER1A, may have implications for neuropsychiatric disorders and its manipulation may represent a novel therapeutic approach.

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**Statement of Ethics**

The authors have no ethical conflicts to disclose.

**Disclosure Statement**

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**Author Contributions**

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