

Protein family review

The Homer family proteins

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Published: 21 February 2007

Genome Biology 2007, **8**:206 (doi:10.1186/gb-2007-8-2-206)

The electronic version of this article is the complete one and can be found online at <http://genomebiology.com/2007/8/2/206>

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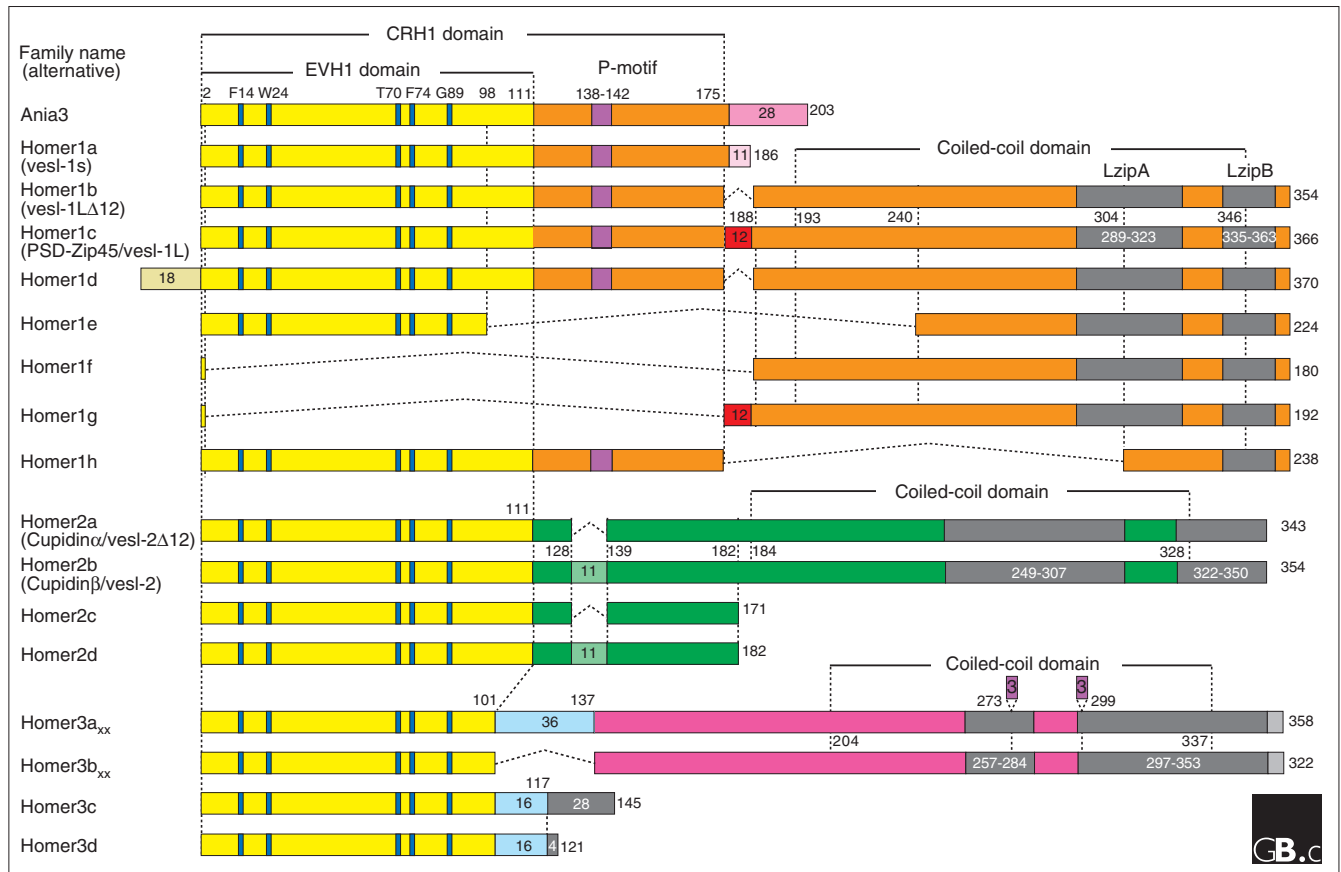
Summary

The Homer family of adaptor proteins consists of three members in mammals, and homologs are also known in other animals but not elsewhere. They are predominantly localized at the post-synaptic density in mammalian neurons and act as adaptor proteins for many postsynaptic density proteins. As a result of alternative splicing each member has several variants, which are classified primarily into the long and short forms. The long Homer forms are constitutively expressed and consist of two major domains: the amino-terminal target-binding domain, which includes an Enabled/vasodilator-stimulated phosphoprotein (Ena/VASP) homology I (EVH1) domain, and the carboxy-terminal self-assembly domain containing a coiled-coil structure and leucine zipper motif. Multimers of long Homer proteins, coupled through their carboxy-terminal domains, are thought to form protein clusters with other postsynaptic density proteins, which are bound through the amino-terminal domains. Such Homer-mediated clustering probably regulates or facilitates signal transduction or cross-talk between target proteins. The short Homer forms lack the carboxy-terminal domain; they are expressed in an activity-dependent manner as immediate-early gene products, possibly disrupting Homer clusters by competitive binding to target proteins. Homer proteins are also involved in diverse non-neural physiological functions.

Gene organization and evolutionary history

The Homer family of adaptor proteins consists in mammals of three members, Homer1, Homer2, and Homer3, all of which have several isoforms as a result of alternative splicing (Figure 1). A short murine Homer, Homer1a (also called vesl-1s, 186 amino acids in length), was the first to be isolated; it is encoded by an immediate-early gene induced in the hippocampus by neuronal activation such as electroconvulsive seizure and long-term potentiation [1,2]. A carboxy-terminal splicing variant very similar to Homer1a, Ania3, was also found as an immediate-early gene induced by dopaminergic stimulation [3]; it has 28 different carboxy-terminal residues in place of 11 residues at the Homer1a carboxyl terminus [4]. By screening for sequence similarity, another class of alternative splicing variants called the long Homer forms were cloned that have longer carboxy-terminal

regions than the short forms: Homer1b and Homer1c (both also called vesl-1L), Homer2a and Homer2b (both also called vesl-2), and Homer3a and Homer3b [5,6] (Figure 1). In parallel, the long Homer forms were also identified as postsynaptic density (PSD) proteins: Homer2a and Homer2b as a developmentally regulated cerebellar PSD protein called Cupidin [7] and Homer1c as a PSD-enriched leucine zipper motif protein called PSD-Zip45 [8]. Several more alternatively spliced variants, Homer1d-Homer1h, Homer2d, Homer3a_{xx}, Homer3b_{xx}, Homer3c and Homer3d, were subsequently detected using reverse-transcriptase PCR [9-11] (Figure 1). The mammalian Homer gene loci are all on different chromosomes: for example, the *Homer1*, *Homer2*, and *Homer3* genes are located on human chromosomes 5q14.2, 15q24.3, and 19p13.11, respectively, and on mouse chromosomes 13C3, 7D3, and 8C1, respectively.

**Figure 1**

Primary structures of Homer family proteins. The conserved amino-terminal EVH1-like domain (which shows 80% sequence similarity between family members) is in yellow. The conserved region of Homer1 (CRH1) [19] and a proline motif (P-motif, 138-Ser-Pro-Leu-Thr-Pro-142) is specific to the mammalian Homer1 subfamily. The carboxy-terminal regions contain coiled-coil and leucine zipper structures and show only 30% sequence similarity among the family members. The coiled-coil regions are in orange, green and pink for the Homer1, Homer2, and Homer3 alternatively spliced forms, respectively. The leucine zipper structures, as predicted by Sun *et al.* [16], are shown as LzipA and LzipB in gray. The nomenclature is from Soloviev *et al.* [9], Saito *et al.* [10], Bottai *et al.* [4] and Klugmann *et al.* [11]. Homer3a_{xx} and Homer3b_{xx} represent the products of four alternative splicing variants, where xx can be 00, 01, 10, or 11 to show the combination of two three-amino-acid insertions (purple) in the coiled-coil domain, as has been suggested for the human forms [9]. Residues involved in ligand contacts are colored light blue.

Orthologs of the Homer proteins have been identified in other animal species: *Drosophila* [12], *Xenopus* [13,14], and zebrafish [15]. Homer proteins have also been predicted from the genome sequences of the chimpanzee, the dog, *Fugu*, and the mosquito. A phylogenetic tree depicting the evolution of the Homer family (Figure 2) suggests that Homer1, Homer2, and Homer3 are found in vertebrates and separated when the fishes first evolved (Figure 2). No homologs have been found from eukaryotes outside the animals.

Characteristic structural features

Homer family proteins share two main structural features: the conserved amino-terminal domain, which is very similar to the Enabled/vasodilator-stimulated phosphoprotein (Ena/VASP) homology 1 (EVH1) domain, and the long Homer-specific carboxy-terminal domain, which consists of a coiled-coil

structure and two leucine zipper motifs [5,6,8,16] (Figure 1). Short Homer forms, such as Homer1a and Ania3, completely lack this carboxy-terminal domain [1-3].

The amino-terminal EVH1-like domain (also called the target-binding or ligand-binding domain) interacts with the proline-rich sequences of the form Pro-Pro-x-x-Phe (where x is any amino acid) that are found in many target or ligand proteins, as listed in Table 1. The carboxy-terminal domain (also called the self-assembly or multimerization domain) of long Homer forms mediates homophilic interactions or heterophilic interactions with different members of the family. Multimers of long Homer proteins, which bind through their carboxy-terminal domains, are thought to act as a protein signaling complex that enables the linkage of various kinds of target proteins in close proximity and thereby facilitates signal transduction among these target proteins.

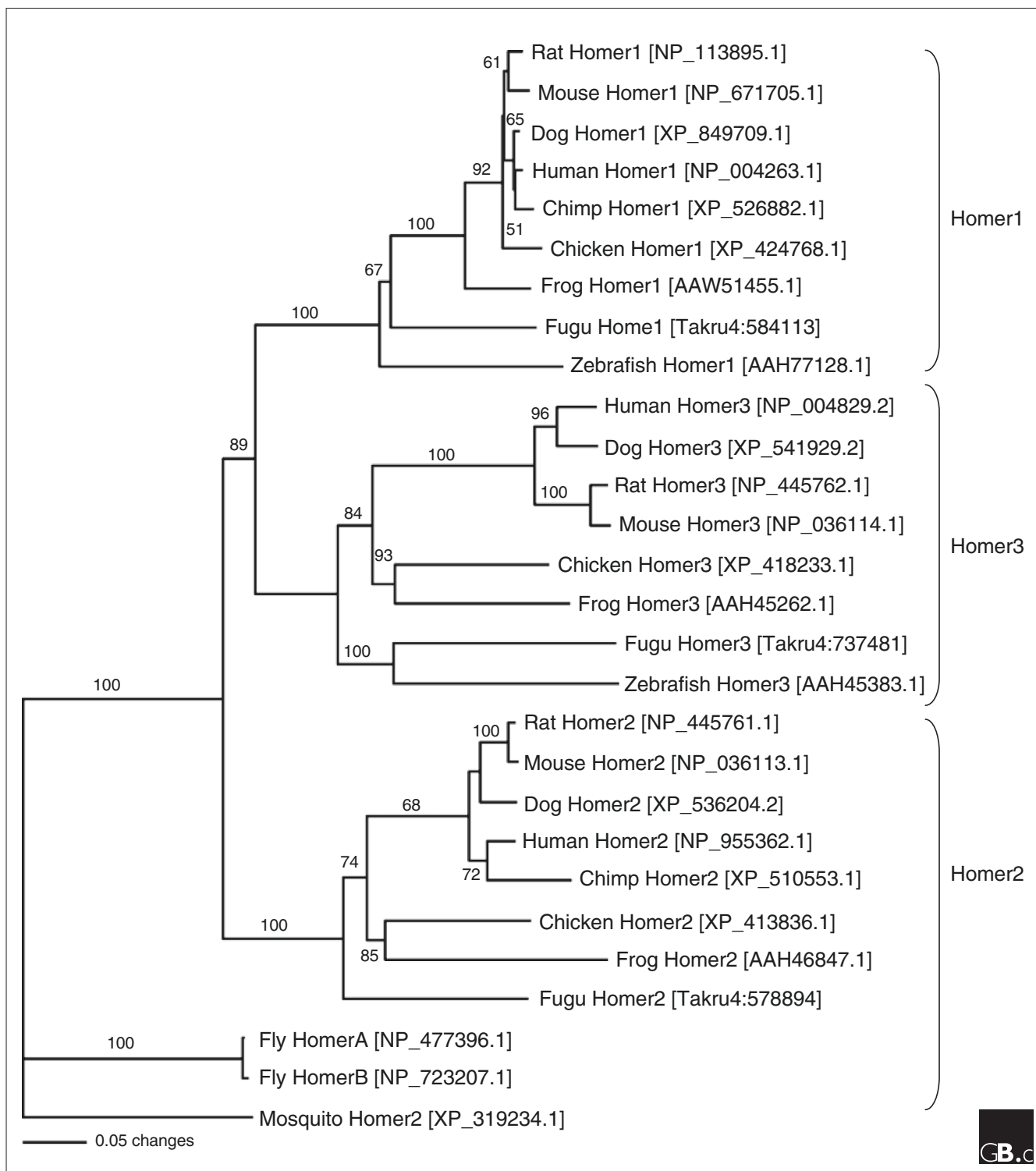


Figure 2

A phylogenetic tree of Homer family proteins. Whole protein sequences of the longest isoform of each family member from human (*Homo sapiens*), chimp (*Pan troglodytes*), dog (*Canis familiaris*), rat (*Rattus norvegicus*), mouse (*Mus musculus*), chicken (*Gallus gallus*), frog (*Xenopus laevis*), Fugu (*Takifugu rubripes*), zebrafish (*Danio rerio*), fly (*Drosophila melanogaster*) and mosquito (*Anopheles gambiae*) were aligned. The accession numbers of the proteins are indicated in brackets. Multiple sequence alignment was performed using CLUSTAL X [70]. Phylogenetic analysis was constructed using the neighbor-joining method [71] using PAUP* version 4.0 beta [72], and the reliability of the tree was estimated by bootstrapping. The tree was rooted with proteins from invertebrates (fly and mosquito). The branch lengths are proportional to the amount of inferred evolutionary change, and numbers between internal nodes indicate bootstrap values as percentages of 1,000 replications.

Table 1**Interaction partners of Homer family proteins**

Protein	Species	Binding sequence or domain	Amino acids	Binding domain of Homer	References
mGluR1a	Rat	Pro-Pro-Ser-Pro-Phe	1146-1150	EVH1	[1,5,6]
mGluR15	Rat	Pro-Pro-Ser-Pro-Phe	1124-1128	EVH1	[1,5,6]
IP ₃ receptor type1	Human	Pro-Pro-Lys-Lys-Phe	49-53	EVH1	[43]
IP ₃ receptor type3	Human	Pro-Pro-Lys-Lys-Phe	48-52	EVH1	[43]
Actin	Mouse	ND	ND	EVH1	[7]
Shank1	Rat	Pro-Pro-Lys-Glu-Phe	1566-1570	EVH1	[64]
Shank3	Rat	Pro-Pro-Glu-Glu-Phe	1310-1314	EVH1	[64]
RyR1	Human	Pro-Pro-His-His-Phe	1772-1776	EVH1	[43]
TRPC1	Human	Pro-Pro-Pro-Phe	645-649	EVH1	[65]
PIKE-L	Rat	Pro-Lys-Pro-Phe	187-191	EVH1	[50]
DynaminIII	Human	Pro-Pro-Val-Pro-Phe	799-803	EVH1	[43,66]
Oligophrenin-1	Human	Pro-Pro-Leu-Glu-Phe	4-8	EVH1	[62]
synArfGEF	Rat		874-981	EVH1	[67]
DrebrinE	Mouse	Pro-Pro-Ala-Thr-Phe	546-550	EVH1	[27]
	Mouse	Pro-Pro-Pro-Val-Phe	628-632	EVH1	[27]
Oskar	<i>Drosophila</i>	ND	ND	EVH1	[57]
C/EBPb	Human	Pro-Pro-Pro-Ara-Phe	16-20	EVH1	[68]
Pax6	Human	Carboxy-terminal Pro-Ser-Thr-rich domain	ND	Homer3 lacking N-terminal 70 amino acids	[69]
Syntaxin-13	Mouse	Carboxy-terminal 153 amino acids	1-153	Homer1b carboxy-terminal 190 amino acids	[21]
Homer1b/c	Mouse	Carboxy-terminal CC	175-366	Carboxy-terminal CC	[5,6,20]
Homer1b/c	Mouse	LZ	289-323, 335-363	Homer1b/c LZ	[8,16]
Homer1b/c	Mouse	Ser-Pro-Leu-Thr-Pro (P motif)	138-142	EVH1	[19]
Homer2	Mouse	Carboxy-terminal CC	112-354	Carboxy-terminal CC	[6,8]
Homer3	Mouse	Carboxy-terminal CC	102-358	Carboxy-terminal CC	[8]
Activated Cdc42	Human	ND	ND	Homer2 CC	[7]

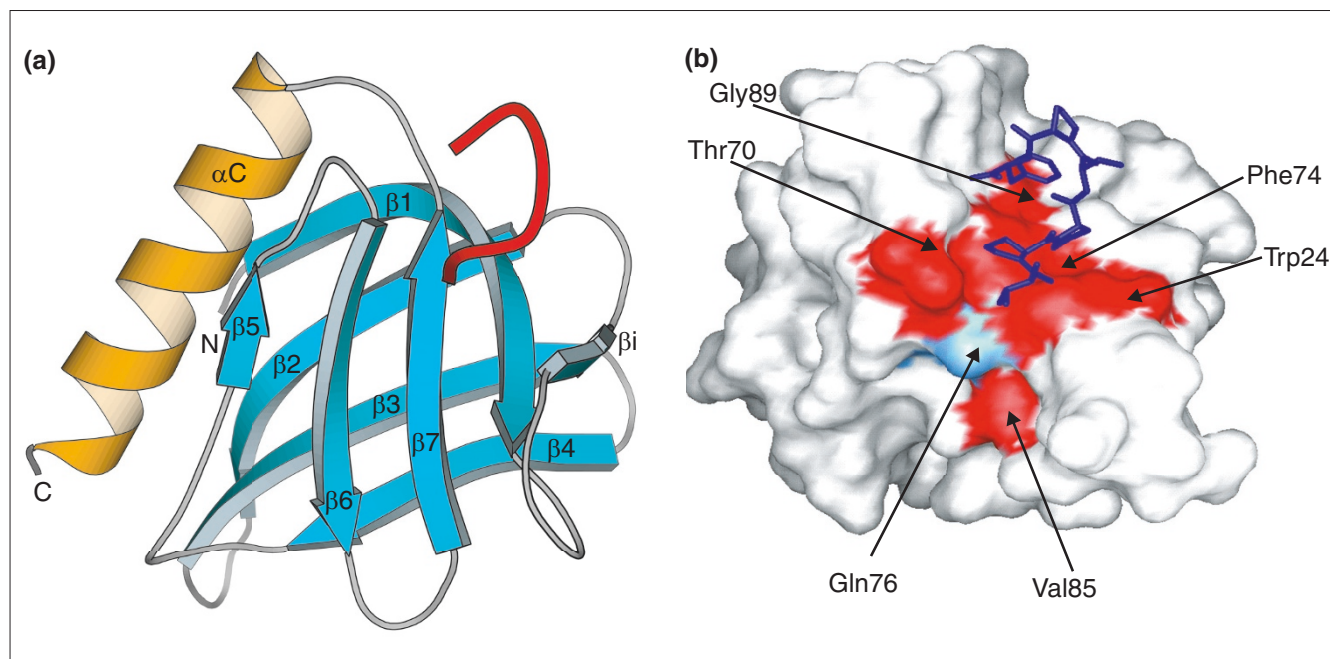
Abbreviations: CC, coiled-coil; C/EBP, CCAAT/enhancer binding protein; IP₃, inositol 1,4,5-trisphosphate; LZ, leucine zipper; mGluR, metabotropic glutamate receptor; PIKE-L, phosphoinositide 3 kinase enhancer; RyR, ryanodine receptor; synArfGEF, guanine-nucleotide exchange factor for ADP-ribosylation factor; TRPC, transient receptor potential channel

The amino-terminal EVH1-like domain

The tertiary structure of the amino-terminal EVH1-like domain has been predicted using X-ray crystallographic analysis (Figure 3) [17,18]. The Homer EVH1-like domain forms a small globular structure that consists of a seven-stranded antiparallel β barrel with a carboxy-terminal α helix packed alongside it. No significant topological differences from the EVH1 domains of mammalian Enabled (Mena) or Ena/VASP can be seen. Interestingly, the consensus motif (Pro-Pro-x-x-Phe) found in proteins that bind to the Homer EVH1 domain has the opposite sequence orientation to the motif found in proteins that bind to the Ena/VASP EVH1 domain (Phe-Pro-Pro-Pro). Both of these proline-rich

consensus peptides seem to form a type II polyproline helix and bind at a distinct binding site on the corresponding EVH1 domain oriented in the same way [17,18]. This distinctive mode of Homer target binding minimizes the potential for cross-reaction with the many other available proline-rich target sequences, although the Homer EVH1 (class II) and other EVH1 domains (class I) seem to be derived from an ancestral polyproline-binding protein [18].

The amino-terminal region containing 1-175 amino acids of mammalian Homer1 proteins is highly conserved and has been called the conserved region of Homer1 (CRH1) [19]. The CRH1 includes the EVH1-like domain and a second

**Figure 3**

The crystal structure of the Homer EVH1 domain [17]. **(a)** Ribbon diagrams of the Homer I EVH1 domain, with five residues of mGluRI (residues 1,146-1,150) as a representative bound ligand in red. The side chains of the adjacent serine and proline in the bound ligand are oriented away from the Homer surface, and the phenylalanine residue forms a unique contact that is not shared by other EVH1 domains (not shown). **(b)** A surface representation of the Homer EVH1 domain, showing the location of residues that are essential (red) and nonessential (light blue) for binding to ligand (dark blue). Reproduced with permission from [17].

proline-containing motif (the P-motif, 138-Ser-Pro-Leu-Thr-Pro-142 in mouse Homer1), which is specific to the mammalian Homer1 proteins. The CRH1 interacts with the neighboring CRH1 in the crystal by intermolecular binding of the P-motif to the EVH1 domain at a site that partly overlaps that used for Pro-Pro-x-x-Phe binding [19]. Given that its binding to the metabotropic glutamate receptor (mGluR) induces the homo-multimerization of Homer1c [8], it is assumed that there are two types of binding of the Homer1 EVH1 domain: binding to the Pro-Pro-x-x-Phe of the target protein and binding to the P-motif of Homer1; the two types of binding induce and arrest this homo-multimerization, respectively.

The carboxy-terminal self-assembly and multimerization domain

Long Homer forms have a characteristic carboxy-terminal region comprising a coiled-coil structure followed by two leucine zipper motifs; this domain can mediate homomeric or heteromeric interactions between long Homer forms [5,6]. Although coiled coils are often implicated in protein-protein interactions, the Homer coiled-coil domain does not interact directly with other coiled-coil proteins, such as dynein [5]. In Homer1c, it is the leucine zipper motifs (ZipA and ZipB) that are involved in the multimerization, and the carboxy-terminal one, ZipB, is crucial [8,16]. Homer1b and Homer3 have been shown to form a tetramer via the

carboxy-terminal domain, including coiled coils and leucine zipper motifs, with no significant involvement of the amino terminal EVH-1 domain and P-motif [20].

An interaction of the carboxy-terminal domains of long Homer forms with other signaling proteins has been indicated. The carboxy-terminal region of Homer1b has been shown to be slightly similar to a mutated in colorectal cancer (MCC)-like domain [6] and to interact with syntaxin-13 [21]. The region of Homer2 from Ser90 to the carboxyl terminus has a weak and fragmentary identity (22%) with a part of Citron, a Rho-effector kinase, including the Rho/Rac-binding site and a part of the leucine zipper motif, and this region interacts with the small GTPase Cdc42 in a GTP-dependent manner [7].

Localization and function

Tissue, cellular and subcellular distribution

Members of the Homer family are predominantly expressed in the nervous system, and they are also expressed in peripheral tissues at low levels. The tissue distribution of the long Homer forms is summarized in Tables 2 and 3. (Most studies have detected the very similar long forms together, so we refer here to 'Homer1b/c', 'Homer2a/b' and 'Homer3a/b' to indicate expression of one or the other or both isoforms of each Homer protein.) In the postnatal developing mouse

Table 2**Homer protein expression in postnatal mouse brain development**

Postnatal week	Homer1b/c				Homer2a/b				Homer3a/b			
	1w	2w	3w	8w	1w	2w	3w	8w	1w	2w	3w	8w
Cerebral cortex	+++	+++	+++	+++	+++	+++	+++	+++	-	-	-	-
Olfactory bulb	++	++	++	++	+++	+++	+++	+++	+	-	-	-
Hippocampus	+++	+++	+++	+++	+++	+++	+++	+++	+	++	++	+
Thalamus	++	++	++	++	+++	+++	+++	+++	-	-	-	-
Midbrain	++	++	++	+	+++	++	++	++	-	-	-	-
Inferior colliculus	++	++	++	+	+++	++	++	++	-	-	-	-
Medulla oblongata	++	++	+	+	+++	+++	+	+	-	-	-	-
Corpus striatum	ND	++	++	++	ND	++	++	++	ND	-	-	-
Cerebellum	++	+	+	-	++	++	+	+	++	+++	+++	+++
Pons	++	++	+	+	+++	+++	++	++	-	-	-	-

Levels of expression are indicated as follows: +++, high; ++, intermediate; +, low; -, not detected; ND, no data.

Table 3**Distribution of Homer protein in mouse peripheral tissues at 2 weeks after birth**

	Homer1b/c	Homer2a/b	Homer3a/b
Thymus	-	-	++†
Heart	+++†	+++†	-
Lung	-	-	+++†
Liver	-	+	-
Kidney	++†	-	+
Spleen	-	-	-
Intestine	-	++†	-
Ovary	++*	-	++*
Testis	++*	-	-
Skeletal muscle	++*	++†	-

Information taken from: * [22]; † [5]; -, not detected.

brain, three long Homer forms are differentially expressed in various regions [22] (Table 2). The retina and spinal cord also express Homer1 [23,24]. The expression level of the long Homer forms in non-neural tissues is very low in comparison with that in the nervous system: the Homer1 and Homer2 long forms are expressed in skeletal and cardiac muscle [5,22,25,26], Homer1b/c in the ovary and testis, Homer2a/b in the liver and spleen, and Homer3a/b in the lung, spleen, kidney and ovary [5,22].

The long Homer family members have distinct cellular distributions in time and space during postnatal development of mouse brain [22]. In the cerebellum, Homer1b/c

and Homer2a/b are predominantly localized at the post-synapses of developing granule cells connecting the mossy fibers in the glomeruli. Homer3a/b is concentrated in the dendritic spines of Purkinje cells connecting the parallel fibers and is also present in their axons. The expression of Homer1b/c and Homer2a/b is regulated reciprocally to that of Homer3a/b in the hippocampus and the developing olfactory bulb; in general, where they are upregulated Homer3a/b is downregulated, and *vice versa*. In the hippocampus, Homer1b/c and Homer2a/b are predominantly localized in the CA1 region and CA1-CA2 region, respectively, whereas Homer3a/b is concentrated in the CA2-CA3 regions.

In fractionation studies on the rodent brain, the long Homer proteins are mainly found in subcellular fractions that are enriched with PSD proteins or postsynaptic membrane proteins [5,7] and in the PSD area of glutamatergic synapses [5,22,27-29] (Figure 4). An axonal distribution of Homer proteins has also been reported, however, with Homer2a/b found in cerebellar Purkinje cells and olfactory neurons [21] and Homer1b/c in *Xenopus* optic tectal neurons [13,14]. Homer1a, a short form, is found at very low levels in hippocampal cells [30,31]. Homer1a is targeted to synapses and regulated in the hippocampus by inducing the inhibition of the ubiquitin-proteasome system [32].

Dynamics of synaptic distribution

The synaptic localization of long Homer forms is not static and becomes dynamic in response to synaptic activity. Postsynaptic clusters of exogenously expressed Homer1c fused to green fluorescent protein (GFP) in cultured hippocampal neurons showed a rapid redistribution and a higher steady-state turnover rate, in response to an increase in intracellular

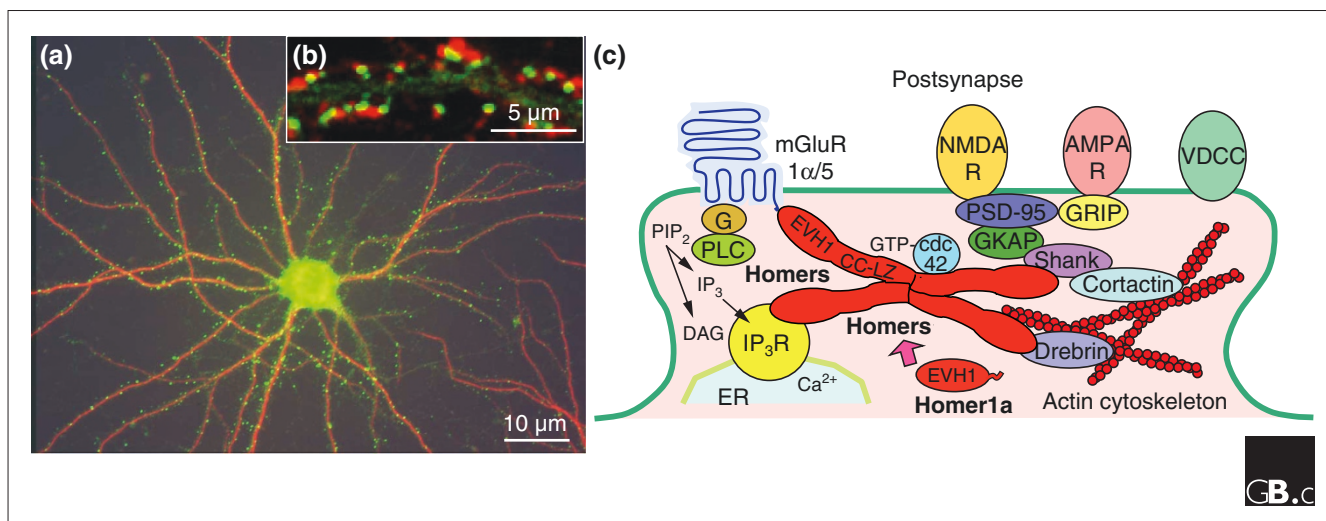


Figure 4

Homer proteins form a physical tether linking signaling molecules in postsynaptic densities. **(a)** Cultured hippocampal neurons co-immunostained for Homer2a/b (green) and the neuronal dendritic marker MAP2 (red). **(b)** Dendritic spines of cultured hippocampal neurons expressing exogenous GFP-Homer2 (green) and immunostained for synaptophysin (a presynapse marker; red). **(c)** A model of the long Homer multimer-mediated postsynaptic protein complex and Homer1a. Long Homer forms (Homers) bind to each other through their carboxy-terminal domains (probably forming a tetramer [20]) and to the target proteins, such as mGluR1 $\alpha/5$, IP₃ receptor, NMDA receptor and Drebrin, to the actin cytoskeleton through their amino-terminal domains, forming a cluster at the postsynaptic density area. Homer1a, which lacks the carboxy-terminal domain, is thought to compete with long Homer forms for binding to target proteins, thus disrupting the cluster. For instance, Homers modulate mGluR-induced intracellular calcium release by linking mGluRs and IP₃R: activation of mGluRs results in the phospholipase C (PLC)-mediated hydrolysis of membrane phosphatidylinositol diphosphate (PIP₂) to diacylglycerol (DAG) and IP₃, which activates the IP₃R to release intracellular calcium. Abbreviations: AMPAR, 5-methyl-4-isoxazolepropionate receptor; CC-LZ, carboxy-terminal coiled-coil structure and leucine zipper motifs of long Homer forms; ER, endoplasmic reticulum; EVH1, the amino-terminal EVH1 domain of Homer; G, G protein; GKAP, guanylate kinase-associated protein; GRIP, glutamate receptor interacting protein; mGluR, metabotropic glutamate receptor; NMDAR, N-methyl-D-aspartate receptor; VDCC, voltage-dependent Ca²⁺ channel.

Ca²⁺ mediated through the activation of N-methyl-D-aspartate receptor (NMDA) receptors or voltage-dependent Ca²⁺ channels [33]. By analysis of GFP fluorescence intensity, it was estimated that the typical single postsynaptic site of cultured hippocampal cells contains 343 ± 57 Homer family proteins [34]. Homer1a, induced by brain-derived neurotrophic factor or a proteasome inhibitor, also causes the redistribution of Homer1c [35]. In cultured cerebellar granule cells, endogenous Homer2 and exogenously expressed GFP-fused Homer2 showed a reversible declustering induced by an NMDA receptor-mediated Ca²⁺ influx followed by activation of a downstream pathway including mitogen-activated protein (MAP) kinases, extracellular signal-regulated kinases (ERKs) and protein tyrosine kinases [28]. This Homer2 declustering is induced before declustering of filamentous (F-)actin and Drebrin (a dendritic actin-binding protein), suggesting that it is independent of the actin cytoskeletal reorganization. The synaptic-activity-dependent dynamics of synaptic long Homer seems to be involved in remodeling the molecular constitution of the PSD protein complex at mature and/or differentiating glutamatergic synapses [28,33].

Targeting of long Homer forms to PSDs seems to be correlated with synaptic contact formation [27] or F-actin

accumulation in PSDs [36]. Newly extended dendrites of cultured hippocampal neurons rapidly acquire Homer clusters, whose density reaches the level of parental dendrites within a few days [37]. Synaptic targeting of Homer is independent of the molecular motor protein myosin Va [29]. Throughout synaptic differentiation of cultured hippocampal neurons, all three long Homer proteins not only form heteromeric co-clusters, but also localize close to NMDA receptor clusters, including those containing the NMDA receptor 2B subunit and PSD-95 [27]. Synaptic Homer clustering is enhanced by simultaneous blockade of NMDA receptor and cAMP phosphodiesterase activities, as is clustering of NMDA receptors [27]. These data suggest a coincidence in developmental and activity-regulated synaptic targeting between Homer and the NMDA receptor complex. This suggests that synaptic targeting of both Homer and the NMDA receptor complex is coincidentally regulated during the development of hippocampal neurons and their activity-dependent synapse formation.

Mechanism

Many of the proteins that bind to Homer proteins are functionally related to one another: for example, mGluR1 $\alpha/5$ and mGluR5 (mGluR1 $\alpha/5$), inositol 1,4,5-trisphosphate (IP₃) receptors (IP₃R), ryanodine receptors, Shank (an adaptor for

the NMDA receptor complex), and transient receptor potential channels are all involved in Ca^{2+} signaling pathways at the PSD. Clusters of long Homer proteins seem to act as PSD signaling complexes through which signal transduction or cross-talk among target proteins is facilitated (Figure 4). Activity-dependent, reversible declustering of long Homer-mediated target protein complexes may be involved in remodeling the target composition of the complex. Homers also associate with the actin cytoskeleton, through which the Homer complex is probably anchored to proper post-synaptic sites.

The short Homer proteins Homer1a and Ania3 are transcriptionally induced only upon neuronal stimulation. They consequently disrupt the scaffolding capability of long Homer forms by sequestering their binding partners. Thus, Homer1a and Ania3 function as natural activity-dependent dominant-negative forms that regulate the scaffolding and signaling capabilities of the long forms. This property seems to be related to synapse and circuit regulation. Indeed, there are several reports demonstrating that Homer1a or Ania3 are upregulated by various physiological treatments that induce synaptic activities: seizure and kindling [2,4], stimulation by light [1], dopaminergic stimulation [4], exploration of a novel environment [38], learning or long-term potentiation [39,40], and administration of psychoactive stimulants or drugs. The signaling cascades involved in the induction of Homer1a expression include the MAP kinase cascade in cerebellar granule cells [41] and the ERK1/2 cascade in hippocampal dentate gyrus cells [42].

Functions in the synapse

Many reports of Homer functions have recently been published; here, we can describe only a fraction of them. Postsynaptic Homer can regulate the synaptic localization of target proteins or the cross-talk signaling among these proteins at the PSD. Homer proteins regulate the activity of mGluR1 α /5 in various ways, including attenuation of its effects by Homer1a, probably as a result of Homer1a's dominant-negative binding [43]; modulation of its linkage to MAP kinase cascades [44]; regulation of its coupling ion channels [45,46]. Homer proteins are thought to act synergistically with Shank, another scaffold protein for the NMDA receptor/PSD-95 complex, via GKAP (guanylate kinase associated protein) in the functional linking of mGluR1 α /5 and IP₃R in the PSD [47]. There seems to be a difference in target-binding affinity or specificity of the EVH1 domain, or other functional properties, among different Homer family proteins [48].

Homer1a expressed in response to neuronal activity regulates synapse function. In cerebellar granule cells, Homer1a induced by NMDA or kainate stimulation triggered the constitutive activity of mGluR1 α /5 independent of binding of an agonist (for example glutamate), but long Homer3 did not show the same activity [48]. Overexpression of Homer1a,

but not of Homer1c, enhanced synaptic transmission in cultured rat hippocampal slices, probably as a result of an increase in synaptic targeting of 5-methyl-4-isoxazole-propionate (AMPA) receptors [40]. In addition, Homer1a enhanced spike-induced Ca^{2+} influx in rat visual cortex pyramidal cells [49]. A recent study showed a role for Homer1a in the attenuation of inflammatory hypersensitivity in spinal cord neurons [24]. Also, the long form of phosphoinositide 3-kinase (PI 3-kinase) enhancer (PIKE-L), a nuclear GTPase that activates nuclear PI 3-kinase, interacts with Homer1c and Homer2a (Table 1), and activation of mGluR1 α /5 enhances formation of an mGluR1 α /5-Homer-PIKE-L complex, leading to activation of PI 3-kinase activity and the prevention of neuronal apoptosis [50].

Cell-surface clustering of mGluR1 α /5

Homer modulates the trafficking of mGluR1 α /5 and its targeting to the membrane. Following heterologous expression in HeLa cells, Homer1b inhibited cell-surface targeting of mGluR5 and induced its retention in the endoplasmic reticulum, whereas Homer1a increased cell-surface mGluR5 [51]. In cerebellar granule cells, exogenously expressed Homer1b also induced intracellular retention of mGluR5 in the endoplasmic reticulum, whereas exogenously expressed Homer1a induced surface clustering of mGluR5 [52]. By contrast, exogenously expressed Homer1b, but not Homer1a, increased cell-surface clustering of mGluR5 and confined its movement within the membrane of cultured hippocampal neurons [53]. Depolarization induced endogenous Homer1a expression through the MAP kinase pathway in cerebellar Purkinje cells, which enhanced cell-surface targeting of mGluR1 α , leading to the increment in mGluR1 responsiveness [54]. These results indicate that the long and short Homer proteins both regulate cell-surface targeting and clustering of mGluR1 α /5, probably by the opposite actions. There are a few differences that seem to be caused by the expression levels of Homer proteins or the cell-type analyzed, however. Because Homer proteins interact with various target proteins, which seem to differ in their number and identity from cell to cell, including membrane proteins and actin-binding proteins, these proteins probably contribute to anchoring the Homer complex at the appropriate intracellular compartments.

Functions in neuronal development

In the developing mouse cerebellum, Homer2 shows a transient increase in the postsynapse of granule cells connecting the mossy fibers and Golgi axon terminals in the glomeruli, and it interacts with the actin cytoskeleton and the small GTPase Cdc42 [7]. Interestingly, the overexpression of exogenous Homer2 inhibits the formation of filopodia-like microspike structures in HeLa cells that is induced by the constitutively active Cdc42 [7]. These results suggest a possible involvement of Homer2 in actin-based synapse morphology. In cultured hippocampal neurons, synapse targeting of exogenously expressed Homer1b is

increased by coexpression with Shank1B, resulting in the enlargement of spine heads (mature mushroom-type spines) and an increase in synaptic currents [55], whereas exogenously expressed Homer1a affects spine morphology (causing a decrease in mature spines but increased elongated processes) [31]. This indicates that Homer1b together with Shank induces spine maturation, and that activity-dependent Homer1a operates in a negative feedback loop to regulate the structure and function of synapses. In addition to the postsynaptic regulation, Homer1b/c regulates axonal path finding of *Xenopus* optic tectal neurons [13].

Homer also has roles in the functions of non-neural tissues. During the differentiation of muscle, Homer2b is up-regulated and seems to increase RyR-mediated Ca^{2+} release, which is necessary for traffic of the transcription factor nuclear factor of activated T cells (NFAT) into the nuclei of the myotube [56]. In pattern formation in *Drosophila* embryos, Homer and another F-actin-binding protein, Bif, show asymmetric localization to the apical cortex of embryonic neuroblasts and may be involved in neuroblast asymmetric divisions by promoting posterior localization of *oskar* mRNA and of proteins that are essential for posterior patterning [57].

Functions in behavior

Several lines of evidence obtained by the disruption or virus-vector-mediated expression of Homer genes demonstrate the involvement of Homer family proteins in animal behavior. Mutation of *Drosophila* Homer caused defects in behavioral plasticity and in the control of locomotor activity, but not in basic neurotransmission. This suggests that Homer regulates the development and function of neural networks underlying locomotor control and behavioral plasticity in *Drosophila* [12]. In an adult rat hippocampus in which exogenous Homer proteins were overexpressed using a recombinant adeno-associated virus gene delivery system, increased levels of Homer1a led to impaired hippocampus-dependent memory, whereas increased levels of Homer1g (which lacks the amino-terminal target binding domain; Figure 1) and Homer1c slightly enhanced memory performance, suggesting that Homer1 splice variants have an active role in behavioral plasticity [11]. Transgenic mice overexpressing Homer1a in striatal medium spiny neurons, in which mGluR1 α /5 is important in synaptic transmission, showed impairments in motor performance and coordination in behavioral tasks and showed repetitive, compulsive behavior (stereotypy) induced by the psychomotor stimulant amphetamine, thereby suggesting a critical role for Homer1 in the modulation of striatal circuits [58].

Homer has been shown to be relevant in drug addiction (reviewed in [59]). Homer2 knockout mice studies showed that Homer proteins are involved in the sensitization of behavior produced by repeated cocaine treatment. Furthermore, the loss of Homer2 induces similar behavioral and

neurochemical phenotypes to those produced by repeated cocaine administration. In addition, both chronic and acute overexpression of constitutive Homer1b and Homer2a/b, but not of short Homer forms, by adeno-associated virus abolished cocaine-induced sensitization of locomotor hyperactivity and prevented the development of glutamate abnormalities in the accumbens. In alcoholism, Homer2 knockout and rescue with adeno-associated virus-expressed Homer2b indicated a necessary and active role for Homer2 in the accumbens in regulating alcohol-induced behavioral and cellular neuroplasticity.

Homer proteins and brain disease

An abnormality of glutamate receptor signaling has been implicated in many different brain diseases, including learning and memory disability, epilepsy, schizophrenia and affective disorder. The genes encoding those Homer family proteins that interact directly with mGluR1 α /5 and indirectly with NMDA receptors at their glutamatergic synapses seem to be candidate genes for involvement in neuropsychiatric phenotypes. Analysis of single-nucleotide polymorphisms in the Homer gene family identified seven, including three in exons, but failed to implicate any of the Homer genes in schizophrenia; these variants remain plausible candidates for other neuropsychiatric phenotypes [60]. A recent study of *Homer1* knockout mice, however, indicated that the loss of Homer1 function causes behavioral abnormalities (motivational, emotional, cognitive and sensorimotor processing) that are consistent with animal models of schizophrenia, and blunts a cocaine-stimulated increase in extracellular glutamate levels in the prefrontal cortex, suggesting reduced activation in this region as the hypofrontality that is commonly observed in schizophrenia [61].

The density and shape of dendritic spines are closely associated with learning and memory performance, and their reduced number and abnormal morphology are observed in the brains of people with various mental disorders. As Homer family proteins regulate spine morphogenesis, the question of whether Homer associates with these dendritic spine defects in mental disorders is intriguing. Oligophrenin-1, a Rho GTPase-activating protein, is absent in a family affected with nonspecific X-linked mental retardation, which is characterized by cognitive impairment. A recent study indicated that oligophrenin-1 has a Pro-Pro-x-x-Phe motif and interacts with Homer1b/c, and that knock-down of oligophrenin-1 expression levels decreases the spine length of hippocampal neurons [62]. Fragile X syndrome is a common hereditary neurodevelopmental disorder associated with mental retardation and is caused by the loss of the RNA-binding protein fragile X mental retardation protein (FMRP). Brains of affected people show an increased density of long and tortuous spines. A recent knockout study revealed that loss of FMRP causes a reduced association of mGluR5 with Homer at the PSD, which is a possible consequence of alterations in synaptic plasticity seen in fragile X syndrome patients [63].

Frontiers

Homer interacts with many different target proteins carrying the Pro-Pro-x-x-Phe consensus motif. There are many other candidate proteins with this motif that have not yet been analyzed and thus should be investigated. In addition, it should be determined whether the Homer family proteins, including alternative splicing variants, have functional differences, for example in their target-binding affinity or preference. Moreover, the structural features of each Homer form, including various protein phosphorylation consensus sites and other putative functional sites (Figure 1), suggest differences in the modulation of these functions.

Long Homer forms are characterized by multimerization through the carboxy-terminal domain. To understand the molecular complexity of target proteins in a long Homer-linked complex, the number of Homer subunits that can assemble in a multimer needs to be determined. Synaptic clustering of long Homer proteins seems to be brought about by preferential anchoring of a few multimers at a specific site or subcellular compartment. The actin cytoskeleton is a candidate for such Homer clustering through actin-associated Pro-Pro-x-x-Phe-containing proteins, such as Drebrin. Moreover, the molecular mechanism underlying the activity-dependent dynamics of long Homer-target clustering is unknown. Declustering of Homer is induced by an increase in intracellular Ca^{2+} concentration through NMDA receptors or voltage-dependent Ca^{2+} channels. Signaling by protein phosphorylation is likely to be involved downstream of this Ca^{2+} signaling. In response to synaptic activity, reversible clustering and declustering of the Homer complex is probably an important mechanism used to alter the molecular composition within the complex, so that cross-talk signaling among cross-linked target proteins can be regulated (Figure 4).

There are still only a few lines of evidence to support the hypothesis that short Homer1a induced in an activity-dependent manner behaves as a natural dominant negative to compete with the target binding of long Homer proteins and to disrupt the long Homer-target protein complex in *in vivo* neurons and within the brain. Other roles for Homer1a can be anticipated (for example, a conformational change of target proteins conferred by the protein-protein interaction), as Homer1a binding induces constitutive activation of mGluR1 α /5 independently of agonist binding [49].

One of the striking features of the expression of the Homer family is that short Homer1a is expressed in an activity-dependent manner and seems to act at the active synaptic site. The mechanism underlying the activity-dependent induction of short Homer1a, in both promoter regulation and alternative splicing, remains to be elucidated. In addition, how the expressed Homer1a is transported to the active synaptic site and what its tag to that site is needs to be investigated.

Homer proteins link many critical synaptic proteins, including those involved in glutamate signaling, which implicates them in many different brain functions and diseases. Genetically engineered Homer mouse models are an important tool with which to clarify the *in vivo* functions of Homer family proteins. As Homer knockout mice show neuropsychologically altered phenotypes, further study of these model mice will shed light on the roles of this interesting protein family in higher brain functions.

Acknowledgements

We thank Dr A. Mizutani (The university of Tokyo) for comments. This work was supported by grant number 18053025 (T.F.) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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