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REVIEW

Structure and function of the guanylate kinase-like domain of the MAGUK family scaffold proteins

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Abstract **Membrane associated guanylate kinases (MAGUKs) are a family of scaffold proteins that play essential roles in organ development, cell-cell communication, cell polarity establishment and maintenance, and cellular signal transduction. Every member of the MAGUK family contains a guanylate kinase-like (GK) domain, which has evolved from the enzyme catalyzing GMP to GDP conversion to become a protein–protein interaction module with no enzymatic activity. Mutations of MAGUKs are linked to a number of human diseases, including autism and hereditary deafness. In this review, we summarize the structural basis governing cellular function of various members of the MAGUKs. In particular, we focus on recent discoveries of MAGUK GKs as specific phospho-protein interaction modules, and discuss functional implications and connections to human diseases of such regulated MAGUK GK/target interactions.**

Keywords MAGUK, GK domain, phospho-protein interaction module, synapse, neuronal disease

Introduction

Membrane-associated guanylate kinases (MAGUKs) originally referred to a family of scaffold proteins highly concentrated at the sites of cell-cell junctions (Woods and Bryant, 1993; Anderson, 1996; Funke et al., 2005). MAGUKs play essential roles in diverse cellular processes, including cell-cell communication, cell polarity establishment and maintenance, and cellular signal transduction (Fanning et al., 1998; Aoki et al., 2001; Tanentzapf and Tepass, 2003; de Mendoza et al., 2010). Since the first member of MAGUK, Disc-Large (DLG), was characterized over 20 years ago (Woods and Bryant, 1991), MAGUKs have expanded to now encompass a large family with very diverse biological functions. Evolutionary survey and phylogenetic analysis of MAGUKs suggest they can be divided into several different classes (te Velthuis et al., 2007; de Mendoza et al., 2010) (Fig. 1). For example, DLG subfamily proteins are widely expressed in the brain and are essential for the formation and plasticity of glutamatergic synapses (Montgomery et al., 2004; Funke et al., 2005; Zheng et al., 2011; Oliva et al., 2012); Zonula Occludens (ZO) subfamily proteins act as molecular linkers between tight junction proteins and actin cytoskeletons (González-Mariscal et al., 2000); calcium/calmodulin-dependent protein kinase (CASK) mainly localizes at the presynapse of excitatory synapses and regulates synaptic vesicle trafficking and neurotransmitter release (Hsueh, 2009; Zheng et al., 2011); palmitoylated membrane protein (MPP) subfamily MAGUKs mainly contributes to cell polarity control (Gosens et al., 2007; Quinn et al., 2009). Other subfamilies of MAGUKs include membrane associated guanylate kinase inverted (MAGI), which is an inverted MAGUK with the guanylate kinase (GK) domain situated at the N terminus followed by two WW domains and five PDZ (PSD-95/DLG/ZO-1) domains; CARMA, a family of caspase recruitment domain-containing proteins, participates in regulation of NF-κB signaling pathways (Blonska and Lin, 2011); voltage-gated calcium channel β subunit ($Ca_v\beta$), a unique member of MAGUKs in that it lacks an N-terminal PDZ domain, modulates calcium channel activities (Fig. 1).

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Domain organization of MAGUKs

By definition, every member of the MAGUK family contains

a guanylate kinase-like (GK) domain, which is the main focus of this review. Additionally, members of the MAGUK family often share several protein–protein interaction modules, including L27 (Lin2/Lin7) domain, PDZ domain, and SH3 domain (Fig. 1).

L27 domain

A number of MAGUK proteins (e.g. CASK, SAP97, MPP2-7) contain L27 domains at their N-termini. The name of the domain was derived from Lin-2 and Lin-7 from *C. elegans*. The domain is now known to play an important role in assembling a number of large protein complexes essential for cell polarity establishment and maintenance (Doerks et al., 2000). L27 domains mediate cell polarity complex assembly via highly specific, heteromeric L27 interactions. For example, the L27 domain of DLG1 (SAP97) forms specific hetero-tetrameric complexes with the first L27 domain (L27N) of CASK (Feng et al., 2004); the second L27 domain (L27C) of CASK also forms a hetero-tetramer with the L27 domain of mLin-7 (Veli or Mals) (Butz et al., 1998; Feng et al., 2005). There appears to be an intrinsic L27 domain complex assembly code, in that a pair of cognate L27 domain complex invariably involves one L27 domain from a single L27 domain-containing protein (e.g. DLG1) and one L27 domain from an L27 tandem-containing protein (e.g. L27N and L27C in CASK) (Roh et al., 2002; Feng et al., 2005). This L27 domain binding code means that a tandem L27 domain-containing protein binds to two different single L27 domain-containing proteins, forming a tripartite L27 domain protein complex. Interestingly, when three such cognate L27 domain proteins are mixed, the four L27 domains form a highly specific, stable, and functionally inter-dependent L27 domain hetero-tetramer (e.g. $L27_{DLG1}$/L27N-$L27C_{CASK}$/$L27_{mLin-7}$) (Olsen et al., 2007; Zhang et al., 2012) instead of an open polymer.

PDZ domain

The PDZ domain is one of the most prevalent protein–protein interaction modules in multicellular eukaryotic genomes. The most common function of PDZ domains is their ability to bind to a short stretch of amino acid residues at the carboxyl termini of target proteins. Additionally, PDZ domains can also bind to internal peptide fragments, although such a mode of PDZ/target interaction is much less frequent. The structural properties of both PDZ domains and PDZ domains in complex with their targets have been extensively reviewed in the past, and readers are referred to several recent reviews (Hung and Sheng, 2002; Zhang and Wang, 2003;Feng and Zhang, 2009). In addition to binding to peptide ligands, PDZ domains can also specifically interact with phospholipids (Mortier et al., 2005; Wu et al., 2007; Chen et al., 2012). Moreover, around 40% of PDZ domains in mammalian proteomes are predicted to contain structured extensions with

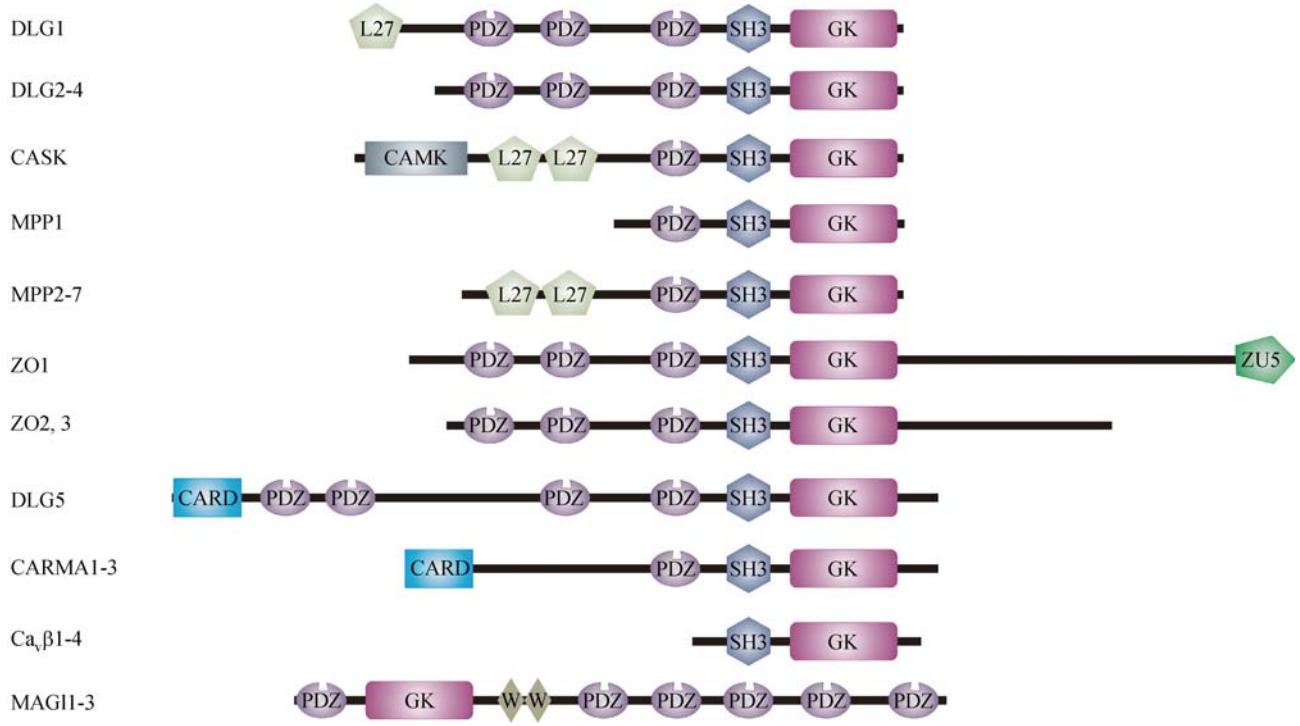

Figure 1 Domain organization of the MAGUK family proteins. All members contain a GK domain with several PDZ domains N and/or C-terminal to the GK domain. All members except for MAGI contain an SH3 domain immediately N-terminal to the GK domain. The CASK and MPP proteins contain a pair of L27 domain connected in tandem in their N-termini. CARMA contains a CARD domain in its N terminus. The $Ca_v\beta$s are the smallest and contain only the SH3 and GK domains.

various sizes and such extension sequences can modulate target binding properties of PDZ domains via a variety of mechanisms (Wang et al., 2010) (summarized in the website: http://bcz102.ust.hk/pdzex/).

SH3-GK tandem

The hallmark of MAGUK family proteins is that all MAGUKs, except for MAGI, share a common structural core consisting of an SH3 domain followed by a GK domain (termed as the SH3-GK tandem). The SH3 domain typically binds to proline-rich sequences such as the PxxP-motif (Yu et al., 1994; Pawson, 2004). However, the MAGUK SH3 domain does not bind to proline-rich sequences; instead, it forms an intramolecular interaction with the subsequent GK domain (McGee and Bredt, 1999; Shin et al., 2000). Structural studies revealed that the SH3 domain and GK domain of the DLG4 (PSD-95) SH3-GK tandem pack with each other, forming an integral structure supramodule in which the last two β strands (βE and βF) of the SH3 domain come from the extreme N- and C-termini of the GK domain (McGee et al., 2001; Tavares et al., 2001; Zhu et al., 2011a)

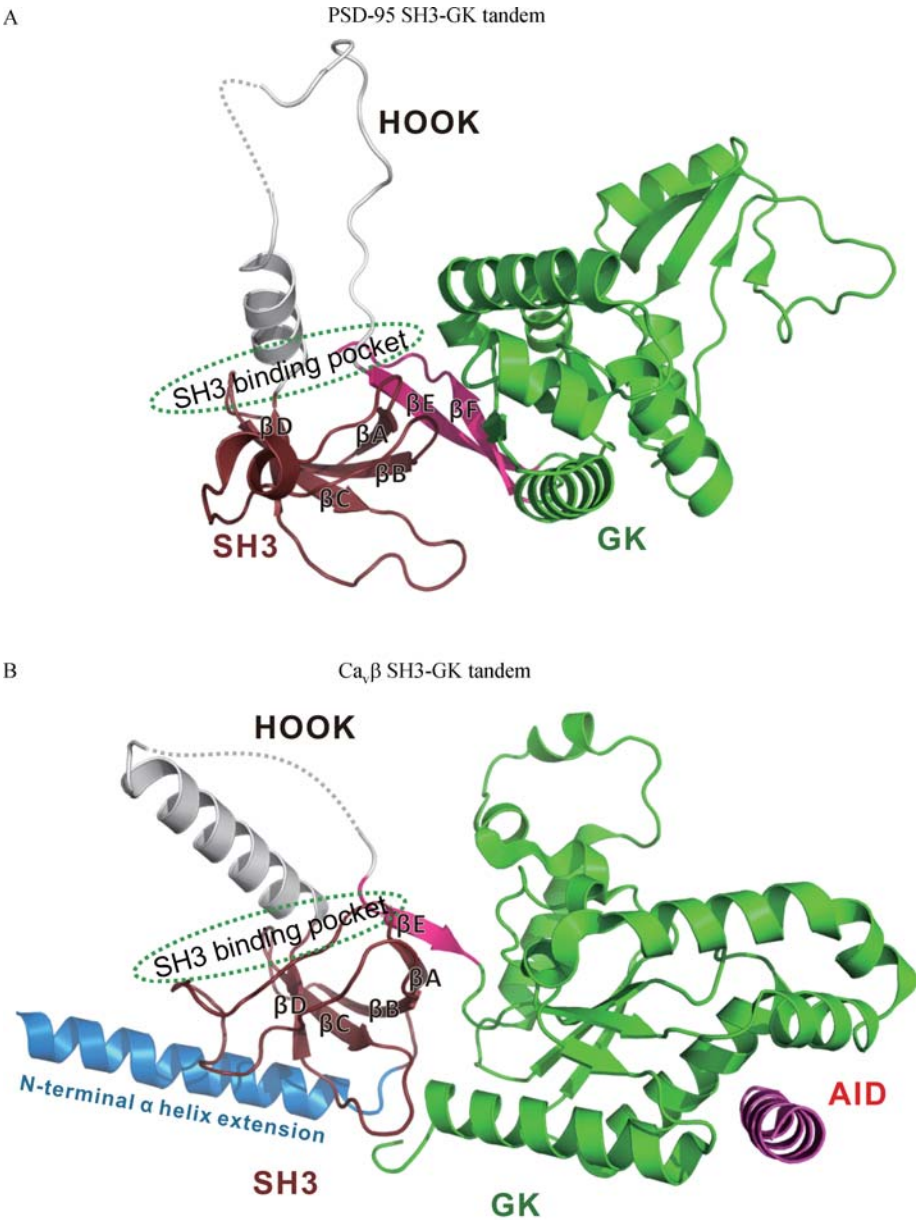

Figure 2 The SH3-GK supramodule. Ribbon diagrams of the PSD-95 SH3-GK tandem (PDB code: 1KJW) (A) and the $Ca_v\beta$ SH3-GK tandem (PDB code: 1T3L) (B). The GK domain, the HOOK region and the split SH3 domain are colored green, gray and ruby-red, respectively. The coupling strands between SH3 and GK domain are colored magenta. The N-terminal helix extension in $Ca_v\beta$ SH3-GK tandem is colored marine-blue.

(Fig. 2A). There is an insertion known as the HOOK region located between the βD and βE strands of the SH3 domain. The structure of the PSD-95 SH3-GK tandem reveals that the HOOK region physically blocks the canonical SH3 target binding site (Fig. 2A), explaining why MAGUK SH3 domains generally do not bind to proline-rich sequences. It is noted that the amino acid sequences of the HOOK regions in different MAGUKs are highly diverse. Accordingly, the HOOK regions of different MAGUKs have been shown to bind to different target proteins including the FERM domain containing protein Band 4.1 (Cohen et al., 1998) and calmodulin (Masuko et al., 1999), although the functional implications of such bindings remain to be uncovered.

The crystal structures of $Ca_v\beta$s show a similar SH3-GK supramodular assembly to that of the PSD-95 SH3-GK tandem (Chen et al., 2004; McGee et al., 2004; Opatowsky et al., 2004; Van Petegem et al., 2004), although obvious differences exist between the two subfamilies of MAGUKs. For example, the $Ca_v\beta$ SH3 domain only consists of five β stands (βA-βE), and lacks the βF found in the PSD-95 SH3-GK tandem (Chen et al., 2004; McGee et al., 2004; Opatowsky et al., 2004; Van Petegem et al., 2004) (Fig. 2B). Similar to that in the PSD95 SH3-GK tandem, βD and βE of the $Ca_v\beta$ SH3 domain are also split by the HOOK region (also known as the V2 domain in $Ca_v\beta$). The canonical target binding site of the $Ca_v\beta$ SH3 domain is also occluded by the HOOK region (Fig. 2B).

The crystal structures of the SH3-GK tandems of PSD-95 and $Ca_v\beta$s, together with structure-based amino acid sequence analysis (not shown here), strongly suggest that formation of an SH3-GK supramodule is a common structural feature of other MAGUK SH3-GK tandems. Currently available cellular and genetic data further indicate that formation of the SH3-GK supramodule is crucial for cellular functions of MAGUKs. For example, a *Drosophila* DLG mutation lacking the last 14 residues (dlg^{sw}), which was predicted to disrupt the SH3-GK tandem formation, is known to be defective in embryogenesis (Woods et al., 1996); several PSD-95 mutant that are defective in their intra-molecular SH3-GK interactions fail to cluster $K_v1.4$ (Shin et al., 2000); a missense mutation (W919R) located near the C-terminal end of CASK GK has been linked to X-linked mental retardation in human and the mutation is also predicted to disrupt the SH3-GK interaction of CASK (Tarpey et al., 2009; Hackett et al., 2010; Moog et al., 2011); direct SH3-GK coupling has also been shown to be crucial for the trafficking of voltage-gated calcium channels and the gating properties of $Ca_v\beta$ (Takahashi et al., 2005).

Moreover, the recently solved structures of the ZO-1 PDZ3-SH3-GK tandem revealed that the PDZ domain directly interacts with the SH3-GK module, forming an integral PDZ-SH3-GK supramodule with distinct target binding properties with respect to the isolated domains (Nomme et al., 2011; Pan et al., 2011). Structure-based sequence analysis suggests that the PDZ-SH3-GK tandems of CARMA, as well as DLG subfamily, are likely to have similar PDZ-SH3-GK supramodular packing interactions. Therefore, the supramodular organization of the PDZ-SH3-GK tandem seen in ZO-1 may be a general property for at least some members of the MAGUK family proteins. It remains to be tested whether the PDZ-SH3-GK supramodule of MAGUKs has any functional implications.

Table 1 Summary of binding partners of MAGUKs GK domains

MAGUKs	Binding protein	Function	References
DLG	LGN	Mitotic spindle orientation in ACD	Zhu et al., 2011
	GKAP/DLGAP/SAPAP	Postsynaptic scaffold protein; involved in OCDs, ASDs	Kim et al., 1997; Zhu et al., 2011
	SPAR	Rap-specific GTPase-activating protein	Pak et al., 2001; Zhu et al., 2011
	AKAP79/150	Adenylate-kinase anchoring protein	Colledge et al., 2000
	MAP1a	A microtubule-associated protein	Brenman et al., 1998
	GAKIN	Kinesin-like motor protein	Deguchi et al., 1998
	BEGAIN	Synaptic scaffold protein	Hanada et al., 2000
	GukHolder	A scaffold protein in synapse	Mathew et al., 2002
CASK	Rabphilin3a	An effector of rab3b GTPase; involved in synaptic vesicular trafficking	Zhang et al., 2001
	Tbr-1	T-box transcription factor	Hsueh et al., 2000
	CINAP	Nucleosome assembly protein; together with Tbr-1 involved in regulation of NR2B expression	Wang et al., 2004
	BCL11	A transcriptional repressor; involved in axon outgrowth and branching	Kuo et al., 2010
	Whirlin	A scaffold protein involved in Usher syndrome	Mburu et al., 2006
MPP1	Gelsolin	Actin capping and severing protein; involved in the actin polymerization in hair cell stereocilia	Mburu et al., 2010
	Whirlin	A scaffold protein involved in Usher syndrome	Gosens et al., 2007
MAGI	GKAP/DLGAP/SAPAP	Postsynaptic scaffold protein; involved in OCDs, ASDs	Hirao et al., 1998
$Ca_v\beta$	$Ca_v\alpha$ AID domain	Modulates gating properties of voltage-gated calcium channels	Van Petegem et al., 2004

GK Domain

The MAGUK GK domain evolved from the enzyme guanylate kinase, which is a member of nucleoside monophosphate (NMP) kinases catalyzing phosphoryl transfer from ATP to GMP (Li et al., 1996). Guanylate kinases are highly conserved from yeast to human, and play critical roles in GMP/cGMP cycling and purine metabolism (Hall and Kühn, 1986). Each guanylate kinase contains three domains called the Core, LID, and GMP binding domains (Stehle and Schulz, 1990; Stehle and Schulz, 1992). The MAGUK GK domain shares ~40% sequence identity to the yeast guanylate kinase. Accordingly, the overall structure of MAGUK GK is highly similar to that of the yeast guanylate kinase (Olsen and Bredt, 2003). Extensive genetic studies have firmly established that the GK domains of MAGUKs are functionally indispensable, although the underlying mechanisms are poorly understood. *Drosophila DLG* is a well-known tumor suppressor and plays crucial roles in the establishment and maintenance of fly epithelia polarity. Mutations leading to truncations of the entire or part of DLG GK are known to cause severe polarity defects of *Drosophila* epithelia. For examples, the dlg^{m52} and $dlg^{X1\text{-}2}$ mutants, which lack the SH3-GK tandem and the GK domain, respectively, cause massive overgrowth of imaginal discs and mutant flies die at the late larval stage. The dlg^{v59} mutant lacks two-thirds of the GK domain, and the mutant fly shows imaginal disc overgrowth and dies at the early pupal period without forming adult cuticle. dlg^{1P20} flies, which harbor a mutant DLG lacking the last 43 aa of GK domain, are defective in neuroblast asymmetric cell divisions and die with severe bristle and eye defects (Woods et al., 1996; Bellaïche et al., 2001). Additionally, a truncation mutation (ARG639TER) of CASK, which leads to the loss of its entire GK domain, has been linked to mental retardation in a human patient with microcephaly (Najm et al., 2008).

Although the MAGUK GK domain shares significant sequence identity with yeast guanylate kinase, the MAGUK GK domain shows very weak binding affinity to GMP and ATP, thus displaying no enzyme activity (Kistner et al., 1995; Hoskins et al., 1996; Kuhlendahl et al., 1998; Olsen and Bredt, 2003). Instead, MAGUK GK domains have evolved into a protein–protein binding module. Many binding partners of MAGUK GKs have been identified in the past (Table 1). These GK domain binding proteins play diverse roles in tissue development, cell polarity control, synaptic formation and plasticity. Despite their well-established functional roles, little is known about the molecular bases governing the bindings of MAGUK GK domains to their targets. Very recently, others and we have discovered that the GK domains of DLG subfamily of MAGUKs bind to their targets in a phosphorylation-dependent manner (Zhu et al., 2011a;Johnston et al., 2012). The structure of SAP97 SH3-GK in complex with a phospho-peptide derived from LGN provides the first glimpse of how MAGUK GK domain has evolved from a GMP to GDP converting enzyme to a specific phospho-protein binding module (Zhu et al., 2011a).

Structural insights into the MAGUK GK/phospho-peptide interaction

Detailed biochemical studies have shown that binding of LGN to SAP97 GK domain requires the phosphorylation of a specific Ser (Ser401 in LGN, Ser436 in the LGN's fly ortholog Pins) in the highly conserved linker region connecting the N-terminal TPR repeats and C-terminal GoLoco motifs (Zhu et al., 2011a). The molecular mechanism governing the interaction between SAP97 GK and a phosphorylated LGN peptide (pLGN) was elucidated by solving the structure of the SAP97 SH3-GK/pLGN complex. The overall structure of the SAP97 SH3-GK tandem is highly similar to that of the PSD-95 SH3-GK structures solved earlier. The pLGN peptide in the complex adopts a one-turn α-helix, followed by a β-strand conformation, and occupies the elongated concave groove formed by the GMP binding subdomain and the Core sub-domain of SAP97 GK (Fig. 3A). The GK/pLGN interface can be divided into two sites: a phospho-Ser binding site (Phospho-site) and a hydrophobic cradle accommodating the C-terminal half of pLGN (Fig. 3B). The phosphate group of pLGN extensively interacts with a number of residues from the GMP binding sub-domain (Arg755, Arg758, Glu761, Tyr767, Tyr791 and Tyr796). Disruption of the interactions in the "Phospho-site" completely abolished the SAP97/pLGN interaction. The amino acid residues forming the "Phospho-site" are highly conserved among most of the MAGUK family proteins including DLG, CASK, MPP and MAGI (Fig. 3C and 3D). Consistent with this analysis, the structures of the GMP binding subdomains of DLG, CASK and MPP1 are highly similar to each other (Fig. 3E). These findings strongly indicate that binding to phosphorylated target proteins is likely to be a common feature for these MAGUK GK domains. It is noted that residues in the hydrophobic cradle are not conserved among the MAGUK GK domains (Fig. 3C and 3D). This may account for target binding specificities among different MAGUK GK domains. Consistent with this, the pLGN peptide binds neither to CASK GK nor to MPP1 GK. The varying spaces between the GMP binding sub-domain and the Core-LID subdomains may also play some role in the target binding specificity among different MAGUK GKs (Fig. 3E).

Analysis of the structures of the SAP97 SH3-GK/pLGN complex, PSD-95 SH3-GK crystalized in the presence of a very high concentration of GMP (Tavares et al., 2001), and the yeast guanylate kinase/GMP complex (Stehle and Schulz, 1990; Stehle and Schulz, 1992) provides a clear clue on how MAGUK GK has evolved from the guanylate kinase enzyme into a phospho-peptide binding module. In the yeast guanylate kinase/GMP complex structure, the phosphate group of GMP forms extensive interactions with a number of residues in the GMP binding site (Arg39, Arg42, Glu45,

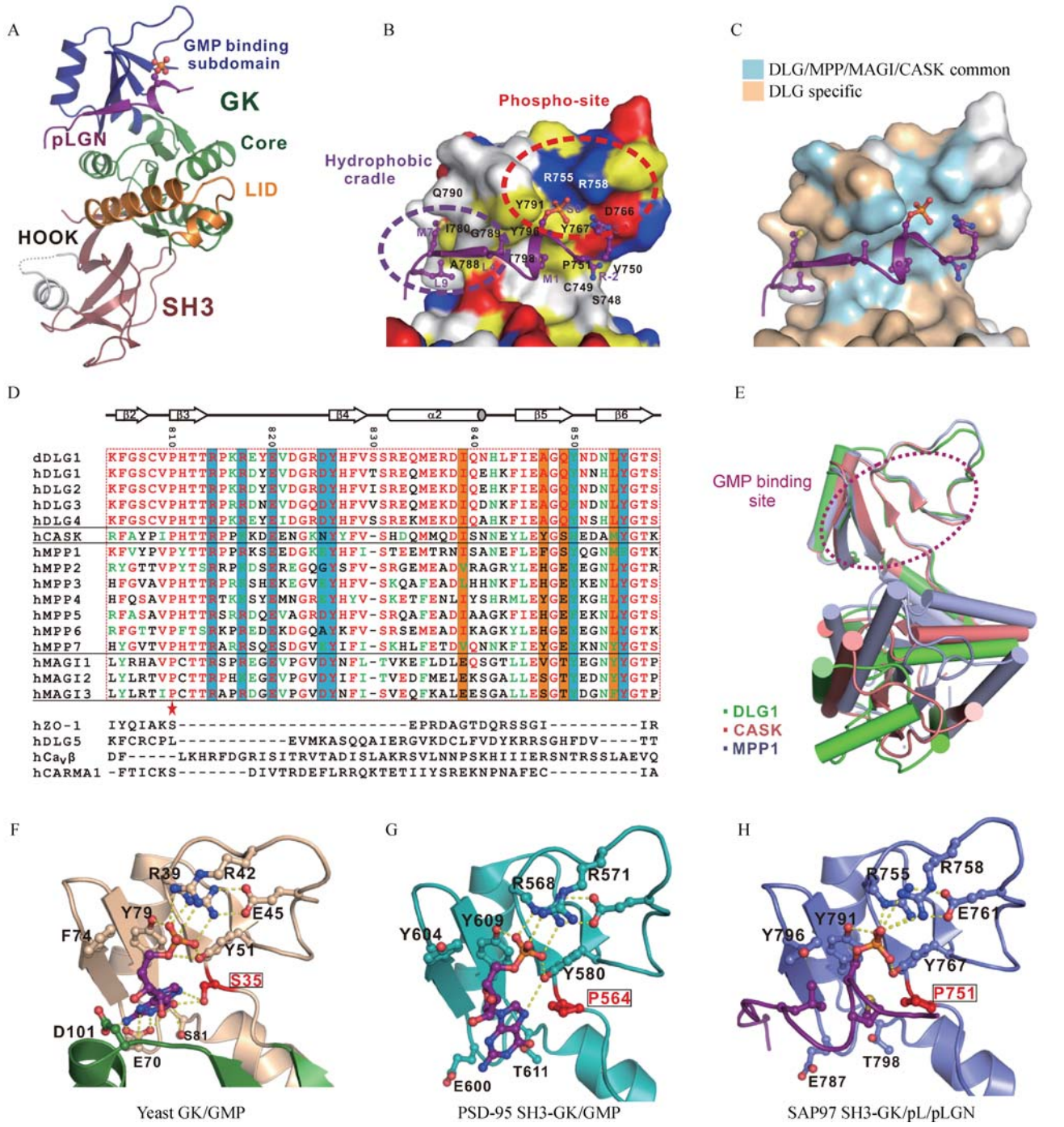

Figure 3 Structural basis of phosphorylation-dependent target binding of MAGUK GKs. (A) Ribbon diagram representation of the SAP97 SH3-GK/pLGN complex. The SH3 domain is shown in ruby-red, the HOOK region in gray, the Core subdomain in green, the LID subdomain in orange, and the GMP binding subdomain in blue. The pLGN peptide is shown in purple with the phosphate group shown in the stick-and-ball model. (B) Surface representation showing the GK/pLGN interface. In this drawing, the hydrophobic residues are in yellow, the positively charged residues are in blue, the negatively charged residues are in red, and the rest of the amino acids are in gray. The phospho-LGN peptide, colored in purple, binds to the "Phospho-site" and the "Hydrophobic cradle" in the GMP binding subdomain of SAP97 GK. (C) The amino acid residue conservation map of various GK domains mapped on to the SAP97/pLGN structure. Residues that are conserved (conservation score > 0.8) in the DLG subfamily are colored beige; residues that are conserved (conservation score > 0.8) among the DLG/MPP/CASK/MAGI subfamilies are colored light blue; other residues are colored light gray. The conservation scores were obtained by the Scorecons Server (Valdar, 2002) based on the amino acid sequence alignment in panel D. (D) Structure-based sequence alignment of the residues of the MAGUK GK GMP binding subdomains. Highly conserved and conserved residues in DLG family are colored red and green, respectively. Residues participating in the phosphate group binding are highlighted in blue-green; residues participating in the hydrophobic cradle binding site are highlighted in orange. (E) Overlay of the GMP binding subdomain of the GK domain structures from MPP1, CASK and DLG1. The GMP binding sites align very well, while the orientations of the core subdomain and LID subdomain vary in different GKs. (F–H) Comparisons of the structures of the yeast guanylate kinase/GMP complex (F), the PSD-95 SH3-GK/GMP complex (G), and the SAP97 SH3-GK/pLGN complex (H).

Tyr51, and Tyr79) and the guanine ring of GMP is coordinated by three critical residues: Ser35, Glu70 and Asp101(Fig. 3F). DLG GKs contain all of the residues corresponding to those involved in binding to the phosphate group of GMP in the guanylate kinase enzyme, and these residues bind to the phosphate group either from GMP or from pLGN following essentially the same pattern as that observed in the yeast guanylate kinase/GMP complex (Fig. 3Gand 3H). However, the corresponding residues interacting with the guanine ring of GMP in the yeast guanylate kinase are missing in DLG GKs (Fig. 3G and 3H), explaining why the GMP binding affinity of PSD-95 GK domain is very low (Olsen and Bredt, 2003). In particular, Ser35 in the link region between the GMP binding and Core domains of the yeast guanylate kinase has evolved into Pro in MAGUK GKs (Pro564 in PSD-95 and Pro751 in SAP97; Fig. 3 G and 3H). This Ser to Pro change not only eliminates two hydrogen bonds between GMP and GK, but also prevents GMP binding-induced closure between the GMP binding sub-domain and the Core sub-domain of MAGUK GKs. Consistent with this analysis, the binding of GMP or pLGN to DLG GKs does not induce obvious overall structural changes to the GK domain (i.e. no inter-domain closure between the GMP binding and the Core sub-domains; Fig. 4B) (Tavares et al., 2001). This is in contrast with the obvious GMP binding-induced, inter-domain closure observed in the yeast guanylate kinase (Fig. 4A). Remarkably, a recent study showed that the yeast guanylate kinase can be converted into a phospho-protein binding module by simply replacing single Ser35 with Pro (Johnston et al., 2011). These recent structural and biochemical studies strongly argue that the MAGUK GK domains have lost their enzymatic activity throughout the evolution to become to phospho-Ser/Thr binding modules. An additional change in DLG GK domains is that the region corresponding to the ATP binding site in the yeast guanylate kinase is blocked by the first helix of the LID sub-domain (Fig. 4B). Accordingly, DLG GK domains have lost their ability to bind to ATP or other potential targets via their ATP binding sites.

Other target binding sites in the MAGUK SH3-GK tandems

The structure of $Ca_v\beta$ SH3-GK tandem in complex with AID (the α-interacting domain) of $Ca_v\alpha_1$ was solved several years ago (Opatowsky et al., 2004; Takahashi et al., 2005; Van Petegem et al., 2004). Overlay of the $Ca_v\beta$ GK domain structure with that of the yeast guanylate kinase shows that the GMP binding sub-domain of $Ca_v\beta$ GK is distorted with missing GMP binding residues (Fig. 4C), indicating that the $Ca_v\beta$ GK domain cannot bind to GMP or phospho-Ser/Thr peptides. However, the ATP binding site in $Ca_v\beta$ GK is retained with a more open conformation compared to that of the yeast guanylate kinase. In fact, the AID peptide of $Ca_v\alpha_1$ forms an α-helix and fits into the ATP binding site through extensive hydrophobic interactions (Fig. 4C). This data suggests that the ATP binding site in the $Ca_v\beta$ GK domain has also evolved into a protein–protein interaction site.

The GK domains of ZO subfamily MAGUKs (ZO-1, 2, 3) are somewhat unique (Fig. 4D). Since the GMP binding site is missing (i.e. ZO-1 GK contains a partial GK fold) and the ATP binding site is blocked by the LID sub-domain (Fig. 4D), ZO-1 GK is not expected to bind to its target proteins following the modes observed in the DLG and $Ca_v\beta$ GK domains. Instead, additional extension sequences such as the U6 regions C-terminal to the GK domain may fold together with the partial GK fold, creating a new target binding site (Fanning et al., 2007; Lye et al., 2010). Future work is needed to test this hypothesis.

Figure 5 summarizes the potential target binding sites (highlighted with dotted circles) available in a MAGUK SH3-GK tandem using SAP97 SH3-GK as the template. The figure shows that MAGUK SH3-GK tandems are highly versatile protein–protein interaction hubs with as many as four different binding sites in each tandem. For example, the DLG, CASK, MPP, and MAGI GK domains use their GMP binding sites to bind to target proteins in a phosphorylation-dependent manner; $Ca_v\beta$ GK uses its ATP binding site to bind to the α-subunit of the channel. The HOOK region between the SH3 and GK domains is also known as a protein interaction site in a number of MAGUK SH3-GK tandems. Although the canonical target binding pocket of the SH3 domain is blocked by the HOOK region in the SH3-GK tandems with known structures, it is hypothesized that binding of target proteins to the HOOK region may release the blockage of the SH3 target binding pocket (Garcia et al., 1998; Maximov et al., 1999).

Functional roles of DLG GK in asymmetric cell division

Stem cells are defined by their abilities to self-renew and differentiate. Asymmetric cell division (ACD) is a particularly attractive strategy that can accomplish both tasks with a single division. Studies of *Drosophila* neuroblasts, which are neuronal stem cells in flies, have generated a wealth of knowledge on the mechanistic bases of ACD. In *Drosophila,* polarized neuroepithelium divides symmetrically within the plane of the neuroectoderm monolayer to expand their pools (Fig. 6A). Upon receiving signals from stem cell niche or neighboring cells, a neuroblast delaminates from neuroepithelium and undergoes ACD to generate two daughter cells of different sizes and fates: a larger apical neuroblast and a smaller basal ganglion mother cell (GMC). The ganglion mother cell will divide once more to generate two neurons or glial cells (Fig. 6B).

Generally, each ACD involves three steps: establishment of apical-basal cell polarity, mitotic spindle orientation, and

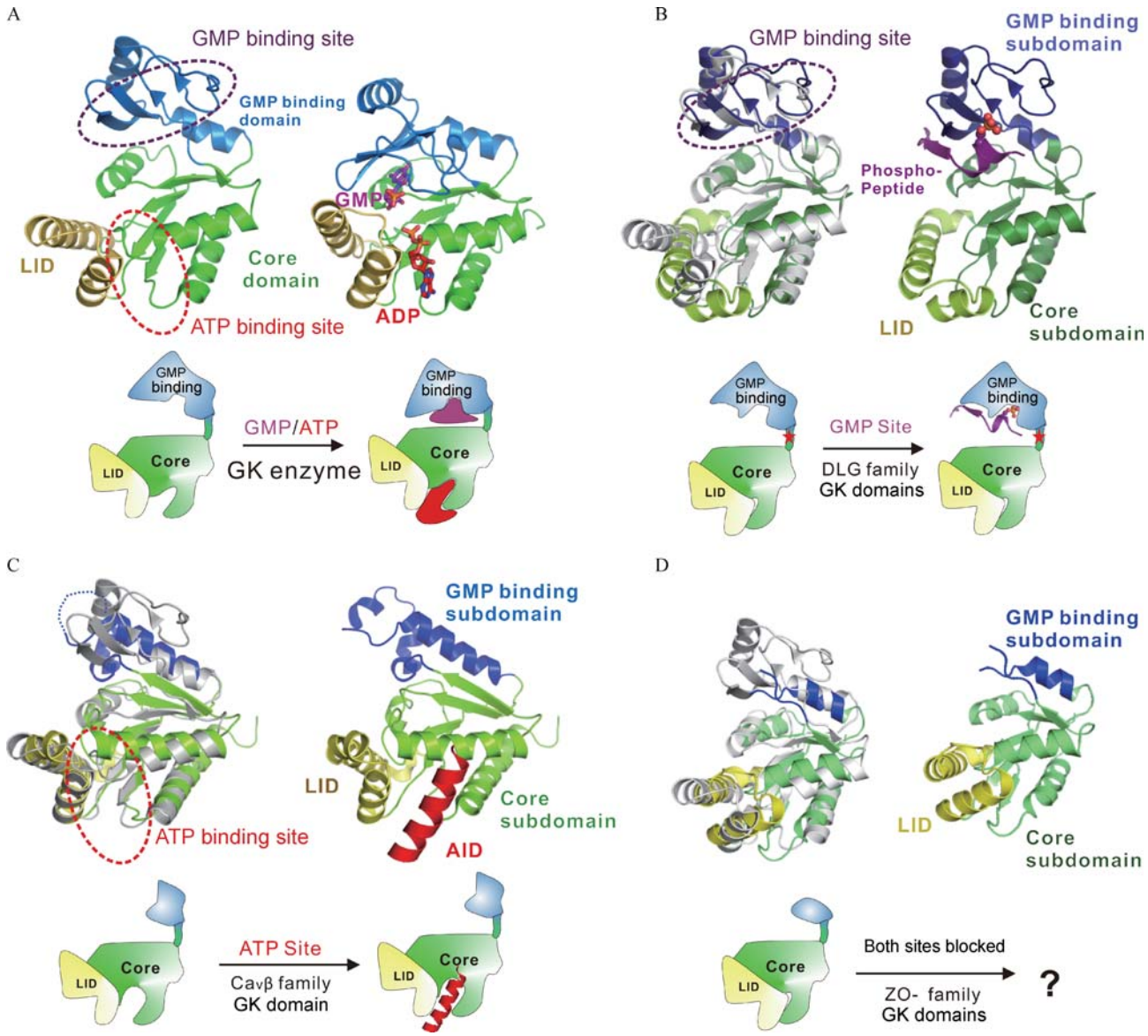

Figure 4 Structural features of the yeast guanylate kinase and several MAGUK GKs. In all of the drawings, the Core subdomain, GMP binding sub-domain and LID sub-domain are colored green, blue and light-orange, respectively. The corresponding cartoon models are shown below. For clarity, each MAGUK GK is individually compared to the yeast guanylate kinase. (A) The GMP, ATP binding sites in the yeast guanylate kinase. (Left) The apo-form of GK kinase (PDB code: 1EX6); (Right) The ADP- and GMP-bound form of GK kinase (PDB code: 1LVG). (B) DLG GK recognizes phospho-peptides via the GMP binding subdomains. (Left) Comparison of the apo-form of DLG GK (PDB code: 1JXO) with the yeast GK kinase (gray) showing that the GMP binding site is retained and the ATP pocket is blocked in DLG GK. (Right) Structure of the SAP97 SH3-GK/pLGN complex (PDB code: 3UAT). The point mutation (S to P) in the link between the GMP binding subdomain and the Core subdomain marked with a red star in the cartoon below. (C) The $Ca_v\beta$ GK domains bind to AID via the ATP binding site. Comparison of the apo-form $Ca_v\beta$ GK (PDB code: 1T3S) with the yeast GK kinase (gray) showing that the ATP binding site is enlarged and the GMP binding site is missing in the $Ca_v\beta$ GK. (D) The GMP binding site is missing and the ATP binding site is blocked in ZO-subfamily MAGUKs. (Left) Superposition of ZO-1 GK (PDB code: 3SHW) with the yeast GK kinase (gray). The function of this GK domain is unknown.

uneven segregation of cell fate determinants (Doe, 2008; Knoblich, 2008; Lu et al., 2000). The cortical polarity of neuroblast is controlled by the conserved apical Par protein complex (Par-3/Par-6/aPKC) and the adaptor protein Inscuteable (Insc). Disruption of the Par/Insc pathway will lead to defects in spindle orientation and mislocalization of cell fate determinants. The Par/Insc pathway sets up the apical-basal polarity during the late interphase and early prophase, then another scaffold protein called partner of inscuteable (Pins) is recruited to the apical cortex via direct Insc-Pins interaction.

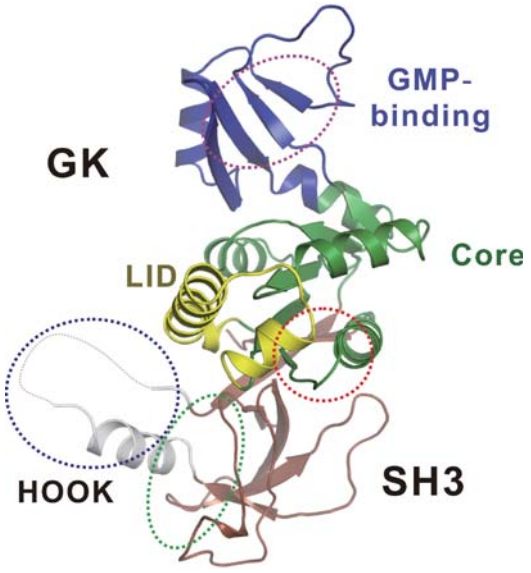

Figure 5 Possible protein–protein interaction sites in MAGUK SH3-GK tandems illustrated on the structure of the SAP97 SH3-GK supramodule. The GMP binding site colored deep purple; the potential ATP binding site colored red; the canonical SH3 binding pocket colored green; The HOOK region binding site colored blue.

Pins then serves as a molecular linker to organize another evolutionarily conserved tripartite complex, Mud/Pins/Gαi (NuMA/LGN/Gαi in mammals), which functions as a receptor independent of the G protein signaling pathway to orient mitotic spindles along the apical-basal axis of each delaminated neuroblast with the help from dynein/dynactin in pulling astral microtubules (Siller and Doe, 2009; Gillies and Cabernard, 2011; Zhu et al., 2011b) (Fig. 6C).

Another set of protein complex composed of Pins/DLG/Khc73 (LGN/SAP97/GAKIN in mammals) was discovered to regulate spindle orientation during ACD (Fig. 6C) (Siegrist and Doe, 2005). This so-called "telophase rescue pathway" is known to be important for coordination between the spindle orientation and the cortical polarity cues. The Pins-mediated spindle orientation is abolished when any proteins in the Pins/DLG/Khc73 pathway is defective (Johnston et al., 2009).

The two conserved pathways (the Mud/Pins/Gαi pathway and the Pins/DLG/Khc73 pathway) ensure correct temporal and spatial assemblies of apical protein complexes to accomplish spindle orientations. Each pathway is activated at a specific time-window during ACD cycle. After the Par/Insc pathway is initiated at late interphase in response to yet still unknown signal(s), Pins/Gαi is recruited to the apical cortex at early prophase via the Insc-Pins interaction. Apical enrichment of DLG occurs after the polarization of the Par/Insc/Pins/Gαi complex, likely due to a phosphorylation-dependent binding of Pins to DLG (Zhu et al., 2011a). The timing of DLG apical localization is precisely matched with the activation of Aurora-A kinase at the start of prophase (Hutterer et al., 2006), and Aurora-A kinase has been shown to phosphorylate Pins at Ser436 (Johnston et al., 2009). The apical cortex attached DLG/Pins complex may serve as an anchor point for the astral microtubules via Khc73-mediated binding to DLG GK (Hanada et al., 2000; Siegrist and Doe, 2005). At this time point, Mud is released from nucleus and forms a stable complex with Pins/Gαi via binding to the Pins TPR repeats. The direct binding between Mud and dynein/dynactin serves to connect the Mud/Pins/Gαi complex at the apical cortex with the astral microtubules, and thus allows the dynein/dynactin-mediated pulling force to be applied toward the apical side of cell cortex during mitosis.

Besides the functional roles in spindle orientation during asymmetric cell division, DLG/LGN/Gαi may also play a role in the regulation of spindle orientation during symmetric cell divisions. In 3D MDCK cultures, maturation of cysts occurs via symmetric cell divisions and this process requires a lateral belt of LGN to position the mitotic spindles to be perpendicular to the apical-basal axis during cell division (Zheng et al., 2010). Since DLG1 is well known to be laterally localized in polarized MDCK cells, it is highly likely that the formation of the lateral LGN belt is mediated by the interaction between the laterally localized DLG1 and phosphorylated LGN (Hao et al., 2010; Zhu et al., 2011a). Thus it is likely that the DLG1/LGN/Gαi complex may function as general machinery in guiding spindle orientations both in asymmetric and symmetric cell divisions.

MAGUK GK-mediated protein complex assembly in synapses

An excitatory glutamatergic synapse is a specialized site of cell-cell contact composed of a presynaptic bouton, a synaptic cleft, and a postsynaptic density (PSD). The presynaptic bouton is filled with numerous neurotransmitter-containing synaptic vesicles (SVs). Once stimulated by an action potential, glutamate will be released from the presynaptic terminal, activating glutamate receptors (such as NMDARs and AMPARs) on the postsynaptic membranes. The PSD, which can be viewed as a membrane-associated mega-organelle and is specialized for postsynaptic signal transduction and processing, contains thousands different proteins packed at an extremely high density. Each PSD forms a disk-like shape structure beneath the postsynaptic membrane with a diameter of ~200–800 nm and a thickness of ~30–50 nm (Fig. 7). MAGUK family proteins play fundamental roles in synapse development and activities by clustering surface glutamate receptors and synaptic adhesion molecules, trafficking receptors and ion channels, modulating cytoskeletal structures, and controlling transmitter release (Montgomery et al., 2004; Funke et al., 2005; Feng and Zhang, 2009; Oliva et al., 2012). In the remaining part of this review, we summarize recent findings of the interactions between the synaptic MAGUK GK domains and their targets and discuss potential functional implications of such interactions.

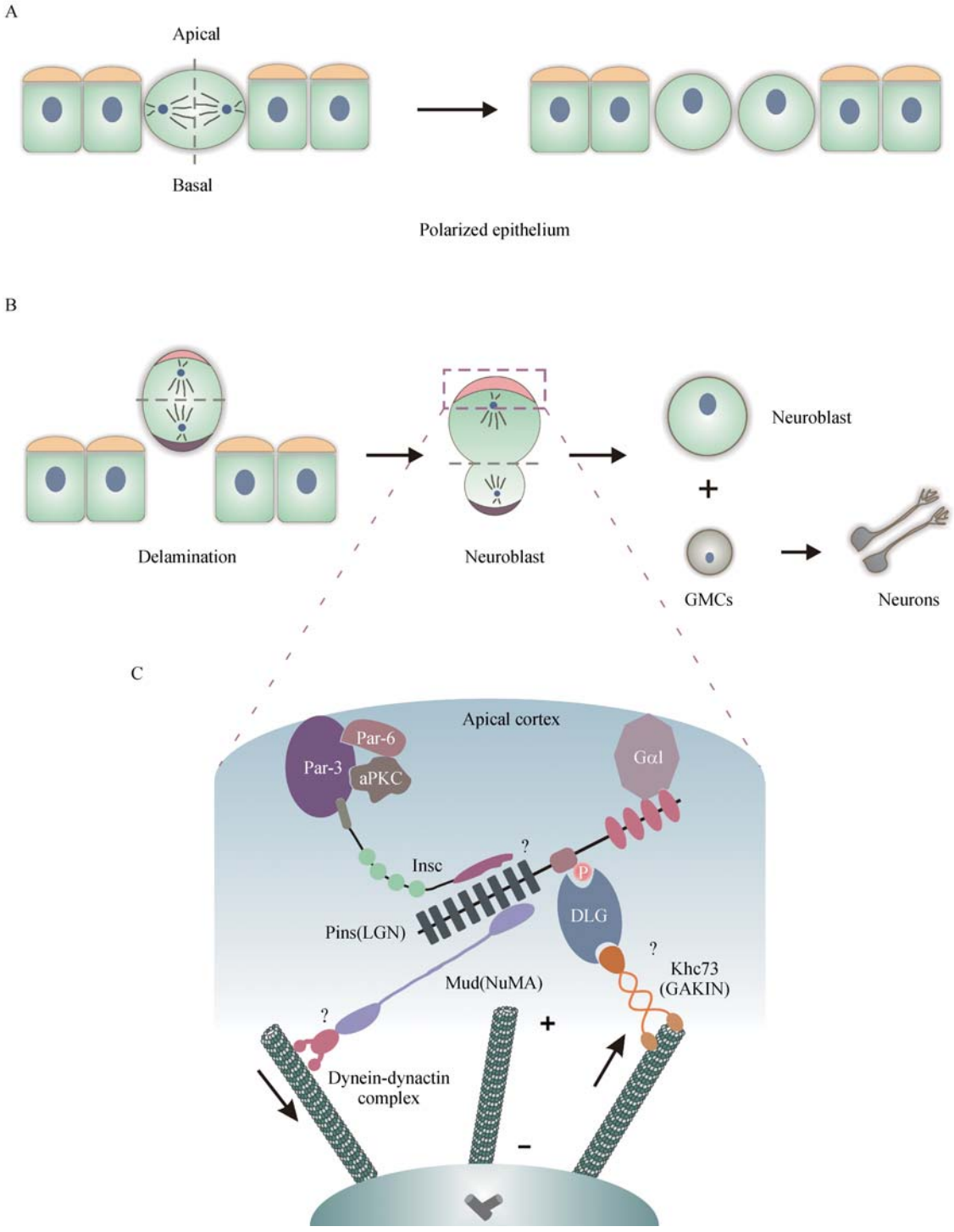

Figure 6 Protein complexes related to the spindle orientation in ACD. (A) In *Drosophila*, polarized epithelium cells divide symmetrically within the plane of epithelium to expand their pools. (B) *Drosophila* neuroblast delaminated from the polarized epithelium undergoes asymmetric cell division to generate a neuroblast and a ganglion mother cell, which divides one more time to give rise to two neurons. (C) A schematic diagram showing several sets of protein complexes that regulate spindle orientations in the *Drosophila* neuroblasts.

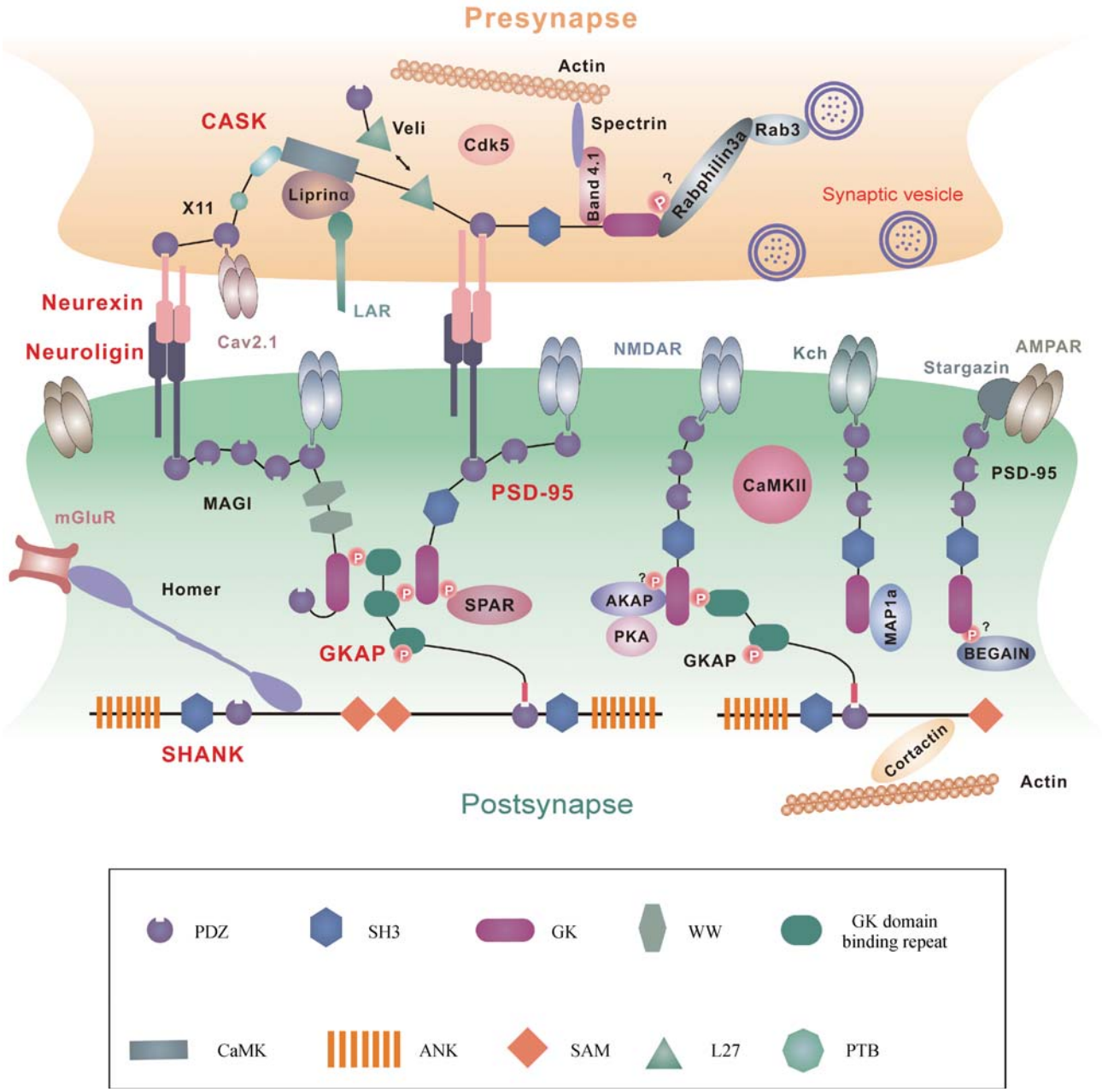

Figure 7 GK domain-mediated protein assemblies in synapses. A schematic diagram showing synaptic signaling complex organization in both pre- and post-synaptic sides of excitatory synapses. For simplicity, only selected sets of synaptic proteins that are directly or indirectly associated with mental disorders are drawn in the figure. The set of proteins labeled in red are known to be high risk factors of ASD.

PSD-95 GK domain-mediated protein complex in synapse

In the past several decades, numerous studies using techniques such as electron microscopy, biochemistry, high-resolution imaging, and proteomics have provided a global picture of the structure and components of the PSD. In general, the PSD can be divided into three layers: the first layer contains membrane receptors, ion channels and transmembrane cell-adhesion molecules; the second layer is enriched with scaffold proteins such as MAGUKs and their interacting proteins and enzymes; the third layer is composed of cytoskeletal proteins (Fig. 7). Protein complexes organized by MAGUKs serve as bridges between the glutamate receptors, downstream signaling proteins and cytoskeleton components, and are central for maturation, activity, and plasticity of synapses. Synapses are highly enriched with

MAGUKs (up to ~10% of total PSD proteins) (Cheng et al., 2006), and most members of the MAGUK family are known to exist in synapses. PSD-95 is the most abundant not only among MAGUKs but also among all scaffold proteins in the PSD. PSD-95 contains three PDZ domains that can bind to various synaptic membrane receptors, ion channels, and synaptic adhesion molecules. The postsynaptic membrane proteins are linked to downstream signaling proteins and the actin cytoskeleton via a highly conserved protein complex composed of PSD-95/GKAP/Shank (Fig. 7). GKAP (also called SAPAP and DLGAP) is a major post-synaptic scaffold protein with an abundance comparable to that of PSD-95 (Cheng et al., 2006). GKAP contains N-terminal five 14 aa-repeats required for binding to PSD-95 GK (Kim et al., 1997; Zhu et al., 2011a), a central region binding to dynein light chain (Naisbitt et al., 2000), and the very C-terminal PDZ binding motif that interacts with the Shank PDZ domain. The proline-rich region and the ankyrin repeats of Shank in turn bind to cytoskeleton-associating proteins cortactin and α-fodrin, respectively (Naisbitt et al., 1999; Böckers et al., 2001). One can envision that PSD-95/GKAP/Shank complex forms a web-like protein network to provide a platform for organizing glutamate receptors, adhesion molecules and their downstream signaling proteins.

Understanding the molecular basis underlying the various interactions in the PSD is extremely important for comprehending the processes involved in synaptic activity and plasticity. A particularly interesting question for this review topic is how the PSD-95 GK-GKAP interaction is mediated. Although the interaction between PSD-95 and GKAP was documented more than 10 years ago, the molecular basis governing the PSD-95 GK/GKAP interaction has remained elusive until a recent discovery from our laboratory (Zhu et al., 2011a). In that study, we discovered that GKAP N-terminal 14 aa-repeats (referred to as the GK binding repeats) bind to PSD-95 GK domain in a phosphorylation-dependent manner. Amino acid sequence alignment analysis of the GK binding repeats of GKAP from different species reveals three absolutely conserved residues including the phosphorylation site Ser (Ser (0), Arg (−3) and Tyr (+1)). These highly conserved residues in the GKAP GK binding repeats can be aligned well with the corresponding residues of the pLGN peptide. A synthetic phosphorylated GKAP peptide binds to PSD-95 GK with an affinity comparable to that of pLGN. Our discovery of the phosphorylation-dependent interaction between PSD-95 and GKAP suggests that the postsynaptic protein complex assembly is a dynamic and regulated event, which is likely to be directly linked to the synaptic activities. Future work is required to confirm whether this interaction is indeed regulated by phosphorylation *in vivo*, and if so, which protein kinases are involved in such phosphorylation event. Curiously, GKAP contains multiple GK binding repeats connected in tandem. Each of such repeats can bind to PSD-95 GK domain with high affinity in a phosphorylation-dependent manner. Multiple GK binding repeats connected in tandem may allow GKAP to respond to graded levels of synaptic activity changes presented in the form of different degrees of phosphorylation of these repeats.

In addition to GKAP, several other synaptic proteins have been reported to bind to PSD-95 GK domain, including SPAR (Pak et al., 2001), AKAP79/150 (Colledge et al., 2000), MAP1a (Brenman et al., 1998), GAKIN (Hanada et al., 2000), and BEGAIN (Deguchi et al., 1998). SPAR is a spine-associated RapGAP that can regulate dendritic spine growth (Lu et al., 2009). SPAR displays actin-reorganizing activity and regulates spine morphology via its GAP and actin-interacting domains (Pak et al., 2001). Interaction of SPAR with PSD-95 physically positions SPAR at the PSD. We demonstrated that the interaction between SPAR and PSD-95 GK also depends on SPAR phosphorylation (Zhu et al., 2011a). MAP1a, a microtubule-associated protein, regulates microtubule dynamics and plays a central role in neuronal morphogenesis. An earlier study, together with our unpublished data, shows that a C-terminal fragment of MAP1a could interact with GMP binding sub-domain of PSD-95 GK (Olsen and Bredt, 2003). Interestingly, unlike the PSD-95/pLGN and PSD-95/pGKAP interactions, PSD-95/MAP1a interaction is not regulated by phosphorylation. Further work is currently undergoing to characterize the PSD-95 GK/MAP1a in detail. Another phosphorylation-independent binding target of PSD-95 GK is the kinesin-like protein GAKIN (also known as kinesin superfamily 13B, KIF13B). As mentioned above, Khc73 (the *Drosophila* counterpart of GAKIN) will form a complex with DLG *in vivo* and *in vitro*, playing important roles in the regulation of spindle orientation in neuroblasts asymmetric cell divisions. Little is known about the exact roles that the PSD-95/GAKIN complex plays in the PSD. It is possible that GAKIN may play a role in the trafficking of PSD-95 to the PSD. In line with this hypothesis, it has been shown that GAKIN is involved in the transport of hDLG to the immune synapses upon activation of T cells (Asaba et al., 2003). Clearly, additional work is needed to characterize the PSD-95 GK/GAKIN interaction in detail.

Other MAGUK GK domain-mediated protein complex in synapse

CASK is another MAGUK family member that mainly localizes at the presynaptic membranes and is known to bind to the cytoplasmic tail of β-neurexins via its PDZ domain (Fig. 7A) (Hata et al., 1996; Sun et al., 2009). CASK mediates additional protein–protein interactions at the presynapse such as assembling the X11/CASK/Veli complex (Borg et al., 1998; Feng et al., 2004), the Caskin/CASK/Veli complex (Tabuchi et al., 2002), and the LAR/liprin-α/CASK complex (Olsen et al., 2005; Samuels et al., 2007; Wei et al., 2011). Additionally, CASK can interact with protein Band 4.1, which in turn is linked to the cytoskeleton via spectrin (Cohen et al., 1998) (Fig. 7). Thus, CASK serves as a master scaffold linking cell adhesion molecules and actin cytoskeleton in

presynapses, and is crucial for proper presynaptic function (Montgomery et al., 2004). Previous studies using yeast two-hybrid screening have identified several binding partners of CASK GK domains. For example, a presynaptic protein rabphilin3a was reported to bind to CASK GK domain *in vitro* (Zhang et al., 2001). Rabphilin3a was originally identified as an upstream effector of rab3b, which is a member of a large family of GTPases mediating directional vesicular trafficking and exocytosis. The interaction between CASK GK domain and rabphilin3a C2 domain (Zhang et al., 2001) raises an interesting hypothesis that CASK might act as a guidance post for targeting synaptic vesicles to specific presynaptic membranes. In addition to assembling multimeric protein complexes in the presynapse, several lines of evidence indicate that CASK may be involved in the regulation of the expression of NMDAR subunit 2B (NR2B) through an interaction between the transcription factor Tbr-1 and CASK GK (Hsueh et al., 2000; Wang et al., 2004; Hsueh, 2009). Molecular details of the CASK/Tbr-1 interaction are still unclear. It is interesting to note that the Tbr-1/CASK interaction complex is regulated by PKA. PKA-mediated phosphorylation of CASK at Thr724 enhances the interaction between CASK and Tbr-1 (Huang et al., 2010). It is possible that the phosphorylation of Thr724 facilitates the entry of CASK into the nucleus for binding to Tbr-1. An alternative possibility is that phosphorylation of CASK at Thr724 causes a conformational change in its GK domain and thus promotes its binding to Tbr-1. The first possibility is more likely, as the T724A-CASK mutant was shown to have a reduced nuclear localization compared to the wild-type CASK (Huang and Hsueh, 2009).

Although structural organization of MAGI is very different from other MAGUKs, its GK domain appears to share many similar biochemical properties with the DLG GKs. For example, MAGI GK has been shown to bind to GKAP with a comparable affinity as PSD-95 GK does (Hirao et al., 1998). However, very little is known about the physiologic roles of the MAGI/GKAP interaction in synapses.

MAGUKs and human diseases

Given the high abundance of and the extensive protein–protein interaction networks organized by different members of the MAGUK family scaffold proteins, it is not surprising that a number of human diseases are associated with the mutations of MAGUKs. For example, the truncation mutations of hDLG3 (SAP102), which lacking the entire SH3-GK tandem, have been linked to severe X-linked mental retardations (Tarpey et al., 2004). The PSD-95/GKAP/Shank complex has come to be an intensely studied topic for their associations with various mental disorders including obsessive-compulsive disorder (OCD) and autism spectrum disorder (ASD) (Geschwind, 2009; Züchner et al., 2009; Peca and Feng, 2012). *Psd-95* gene disruption in mice induces behavioral and molecular abnormalities reminiscent of ASD and Williams syndrome in humans (Feyder et al., 2010). Recent studies found that the *sapap3* mutant mice showed increased anxiety-like behavior that is similar to human OCD (Welch et al., 2007; Bienvenu et al., 2009). Genetic disruptions of *shank2* or *shank3* in mice led to compulsive behavior and impaired social activity, resembling two of the common clinical features of ASD (Durand et al., 2007; Moessner et al., 2007; Bangash et al., 2011; Peça et al., 2011; Schmeisser et al., 2012).

Mutations in *CASK* have been found in patients with X-linked mental retardation (XLMR), microcephaly, optic atrophy, and brainstem and cerebellar hypoplasia (Froyen et al., 2007; Hayashi et al., 2008; Najm et al., 2008; Piluso et al., 2009; Tarpey et al., 2009). Among the disease mutations, a number of them are truncation mutations that result in complete loss of CASK GK. Additionally, several missense mutations are located in the CASK SH3-GK tandem (e.g. the W919R mutation discussed earlier on). Several mutations in the HOOK region of CASK (D710G and Y728C) may disrupt the interactions with their targets (Tarpey et al., 2009; Hackett et al., 2010; Moog et al., 2011).

Mutations of MPP1 (p55) are known to be linked to the Usher syndrome, which is the most common and severe form of hereditary loss of hearing and vision (Mburu et al., 2006; Pan and Zhang, 2012). MPP1 can form a complex with whirlin via the binding of MPP1 GK to whirlin PDZ domain at the stereocilia tip of hair cells and retina (Mburu et al., 2006; Gosens et al., 2007). Again, the mechanistic basis of the MPP1 GK/whirlin interaction is poorly understood.

Conclusions and perspectives

In the past few years, substantial progress has been made in unveiling roles of MAGUK GK domain-mediated protein assemblies in diverse cellular processes. The recently solved atomic structure of the SAP97/pLGN complex has shed light on the mechanistic basis of how MAGUK GK domains recognize their target proteins with high affinity and specificity and in a regulated manner. The discovery of the MAGUK GK domain as a phospho-Ser/Thr binding module also expands the repertoire of the phospho-Ser/Thr binding modules (Yaffe and Elia, 2001).

A number of important issues concerning MAGUK GKs need to be addressed in the future. These issues include whether MAGUK GK domain binders are indeed phosphorylated *in vivo*; which kinases are involved in the phosphorylation of these MAGUK GK targets; how the synaptic activities are connected to the dynamic interactions between MAGUK GKs and their targets; whether perturbations of MAGUK GK-mediated synaptic protein interactions are linked to mental disorders such as autism; how to manipulate the MAGUK GK-mediated synaptic protein interactions with low molecular weight compounds for potential therapies of

mental disorders and other human diseases. We are confident that many exciting new findings will emerge in the above areas in the next 5–10 years.

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