Kidins220/ARMS as a functional mediator of multiple receptor signalling pathways

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Journal of Cell Science

Summary

An increasing body of evidence suggests that several membrane receptors – in addition to activating distinct signalling cascades – also engage in substantial crosstalk with each other, thereby adjusting their signalling outcome as a function of specific input information. However, little is known about the molecular mechanisms that control their coordination and integration of downstream signalling. A protein that is likely to have a role in this process is kinase-D-interacting substrate of 220 kDa [Kidins220, also known as ankyrin repeat-rich membrane spanning (ARMS), hereafter referred to as Kidins220/ARMS]. Kidins220/ARMS is a conserved membrane protein that is preferentially expressed in the nervous system and interacts with the microtubule and actin cytoskeleton. It interacts with neurotrophin, ephrin, vascular endothelial growth factor (VEGF) and glutamate receptors, and is a common downstream target of several trophic stimuli. Kidins220/ARMS is required for neuronal differentiation and survival, and its expression levels modulate synaptic plasticity. Kidins220/ARMS knockout mice show developmental defects mainly in the nervous and cardiovascular systems, suggesting a crucial role for this protein in modulating the cross talk between different signalling pathways. In this Commentary, we summarise existing knowledge regarding the physiological functions of Kidins220/ARMS, and highlight some interesting directions for future studies on the role of this protein in health and disease.

Key words: Kidins220/ARMS, Neuronal differentiation, Neurotrophins, RTK signalling, Synaptic plasticity

Introduction

The correct development of the nervous system relies on the ability of axons and dendrites to recognise their targets. During this highly regulated process, neurons migrate and form functional connections in response to gradients of growth factors that regulate multiple neuronal functions, including cell survival, differentiation and synaptic plasticity (Bibel and Barde, 2000; Chao, 2003; Huang and Reichardt, 2003). The neurotrophin (NT) family is one of the best-characterised groups of neurotrophic factors and includes nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), and neurotrophin-3 (NT3) and -4 (NT4, also known as NT4/5) (Huang and Reichardt, 2001). Neurotrophins bind with high affinity to three related tropomyosin receptor kinases (Trks): NGF binds mainly to TrkA, whereas BDNF and NT4/5 bind mainly to TrkB, and NT3 to TrkC. In addition, all neurotrophins also bind to the p75 neurotrophin receptor (p75[NTR], also known as NGFR), a member of the tumour necrosis factor (TNF)-receptor superfamily (Bibel and Barde, 2000). Other growth factors that are paramount in neuronal growth and development are the glial-cell-line-derived neurotrophic factor (GDNF), which acts through the Ret tyrosine kinase receptor, and the GDNF family receptor α (GFRα) (Paratcha and Ledda, 2008). In addition, trophic factors such as the VEGF and the ephrin–ephrin-receptor (ephrin–Eph) families have crucial roles both inside and outside the nervous system (Klein, 2009; Ruiz de Almodovar et al., 2009).

The vast majority of these ligands perform their physiological functions through plasma membrane receptors that have tyrosine kinase activity – the receptor tyrosine kinases (RTKs) – which results in distinct signalling outputs and cellular effects. However, how RTKs mediate such diverse biological outcomes by starting from a common subset of signalling molecules – such as the Ras protein family, the extracellular regulated kinases (ERKs; also known as mitogen activated protein kinases, MAPKs), Akt and phospholipase Cγ (PLCγ) – is presently unclear. The signal specificity of NT receptors is tuned by a number of factors, including the repertoire of Trk receptors and the level of p75[NTR] expressed by a particular neuron, which determine the subset of neurotrophins to which a particular neuron would respond (Clary and Reichardt, 1994; Strohmaier et al., 1996; Hapner et al., 1998; Palko et al., 1999; Stoilov et al., 2002). Upon binding of NTs, Trk receptors dimerise and cross-phosphorylate each other. Activated Trk receptors are then able to recruit a number of adaptors through their phosphorylated residues. At the intracellular level, availability of different substrates or adaptors could, thus, control signalling downstream of Trk receptors (Lee et al., 2001). Additionally, the response to neurotrophin signals depends on the temporal and spatial pattern of stimulation. Thus, transient or sustained activation of the MAPK, phosphoinositide kinase-3 (PI3K) or Akt pathways mediates distinct cellular effects, for example by promoting a local and fast response at the growth cone compared with a slower response at distal sites, such as the

soma (Marshall, 1995; Kuruvilla et al., 2000; Watson et al., 2001). To add a further level of complexity, different receptors can interact with each other. For example, p75[NTR] is found in complex with Trk, sortilin-1 (Sorl1) or Nogo (RTN4R) receptors (Bronfman and Fainzilber, 2004), whereas TrkB interacts with ephrin-A7 and EphA5 (Fitzgerald et al., 2008; Marler et al., 2008). Similarly, GDNFαR, Ret tyrosine kinase and protocadherins cooperate to regulate neuronal survival (Schalm et al., 2010), and the interaction between EphB and N-methyl-D-aspartate (NMDA) receptors – an important class of glutamate receptors – is crucial for the modulation of synaptic plasticity (Dalva et al., 2000; Henderson et al., 2001). Thus, a complex interplay between the repertoire of receptors and the availability of downstream effectors ultimately determines the response of a neuron to a given stimulus.

A common downstream effector of these pathways is the scaffolding protein Kidins220/ARMS. In mice, embryos that lack Kidins220/ARMS die at birth, indicating that this protein is essential for life. In addition to a variety of neuronal phenotypes, these embryos show severe defects in vascular development and cardiac malformations, which are likely to be the cause of death (Cesca et al., 2011; Cesca et al., 2012). Mutants of Kidins220/ARMS have been described in *Caenorhabditis elegans* (tag-114) and *Drosophila melanogaster* (Dmel\CG42672) (see also http://www.wormbase.org/ and http://flybase.org/). However, only a partial phenotypic characterisation of these mutants has been provided so far, making the analysis performed in mice the most informative to date.

Kidins220/ARMS is a multifunctional scaffolding protein

Kidins220/ARMS was initially identified as a substrate for protein kinase D (PKD) in neural cells (Iglesias et al., 2000), and independently characterised as a downstream target of the signalling mediated by neurotrophins and ephrins (Kong et al., 2001). Kidins220/ARMS is an integral membrane protein, containing four transmembrane segments in the central part of the molecule, and N- and C-terminal tails both exposed to the cytoplasm (Fig. 1). Sequence analysis of Kidins220/ARMS revealed the presence of numerous domains that mediate protein–protein interactions. The N-terminus of Kidins220/ARMS contains eleven ankyrin repeats (residues 37–398 in the mouse sequence), which form a concave binding surface that is accessible to molecular partners, such as the Rho–guanine nucleotide exchange factor (RhoGEF) Trio (Neubrand et al., 2010). Kidins220/ARMS has been included in the Kidins220/ARMS and PifA (KAP) family of P-loop nucleotide phosphatases (NTPases). P-loop NTPases contain Walker A and Walker B motifs (WA and WB, respectively) (Higgins et al., 1988), which are often involved in the binding of nucleotides and have been identified in the juxtamembrane regions flanking the N- and C-terminus of Kidins220/ARMS. Members of this family are predicted to mediate the assembly of protein complexes that are associated with the inner surface of cell membranes (Aravind et al., 2004). Interestingly, Kidins220/ARMS binds ATP (Teresa Iglesias and G.S., unpublished), although a functional role for its Walker motifs has so far not been established. Thus, further work is required to establish whether Kidins220/ARMS
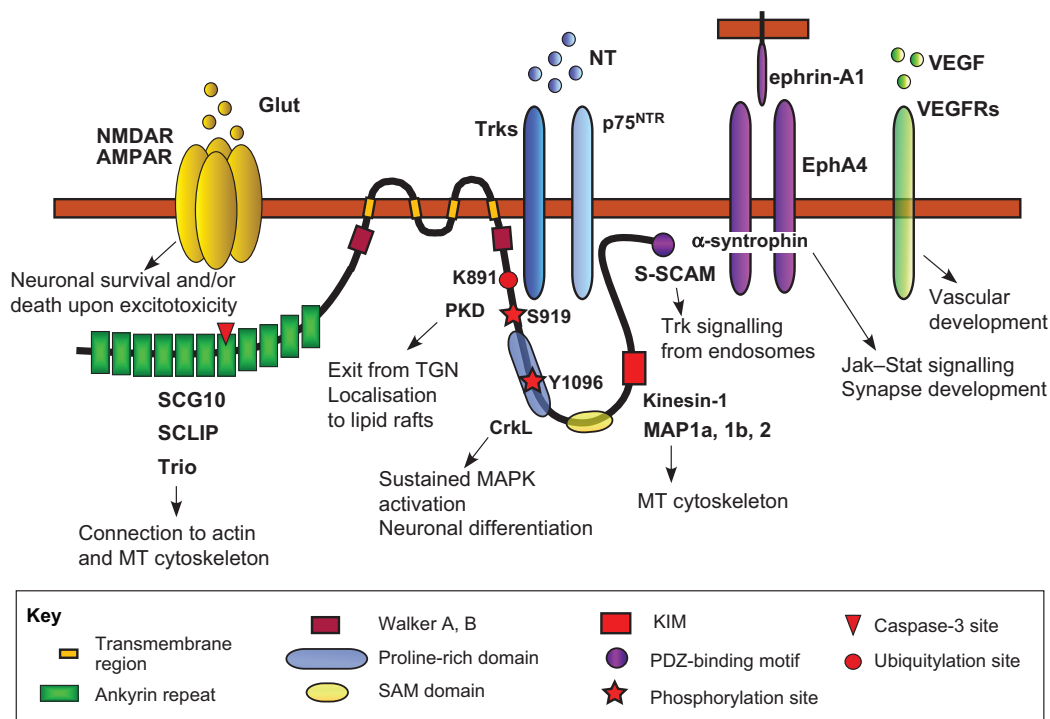

Fig. 1. Kidins220/ARMS engages in multiple protein–protein interactions. Schematic structure of Kidins220/ARMS with its different domains and sites of post-translational modifications. Also shown are the molecular partners identified to date, together with the cellular events that are triggered by their binding to Kidins220/ARMS (arrows). The domains of Kidins220/ARMS mediating the interaction with the various partners are listed in Table 1. AMPAR, AMPA receptor; Glut, glutamate; MT, microtubule; NT, neurotrophins, NMDAR, NMDA receptor.

has a detectable NTPase activity, or whether ATP binding is required for its function.

The C-terminus of Kidins220/ARMS includes several protein–protein interaction domains; for example a proline-rich region (residues 1080–1092) that binds the adaptor protein CrkL (Arevalo et al., 2006), and a sterile alpha motif (SAM; residues 1231–1300) (Iglesias et al., 2000; Kong et al., 2001) that might be involved in both inter- and intra-molecular interactions. In addition, the kinesin light chain (KLC)-interacting motif (KIM) (residues 1387–1426) binds the kinesin-1 motor complex (Bracale et al., 2007). The last four amino acids of Kidins220/ARMS constitute a PDZ-binding motif that binds the PDZ domain of α-syntrophin, thereby forming a complex that is associated with the EphA4 receptor at the neuromuscular junction (Luo et al., 2005).

The observation that Kidins220/ARMS interacts with all three Trk receptors and with p75[NTR] (Arevalo et al., 2004; Chang et al., 2004) prompted a series of studies on the role of Kidins220/ARMS in various aspects of neurotrophin physiology, mostly focusing on the molecular mechanisms by which Kidins220/ARMS mediates Trk signalling (Arevalo et al., 2004; Arevalo et al., 2006). With its multiple domains, Kidins220/ARMS is a well-suited candidate to act as a signalling platform, by recruiting cell-specific adaptors and effectors to activated Trk receptors. Kidins220/ARMS is also involved in functional interactions with several other receptors, such as glutamate, Eph and VEGF receptors (VEGFRs) (Luo et al., 2005; Lopez-Menendez et al., 2009; Arevalo et al., 2010; Cesca et al., 2012), thus representing an example of how different trophic pathways can converge and, possibly, be integrated at the level of a single adaptor molecule. A list of the Kidins220/ARMS interactors identified to date is presented in Table 1.

Kidins220/ARMS in evolution

Bioinformatic analysis revealed Kidins220/ARMS orthologues in several metazoans (Fig. 2A; Table 2) [(Iglesias et al., 2000; Kong et al., 2001) and (Probir Chakravarty, unpublished)]. In a phylogenetic tree, mammalian, avian and reptilian proteins are clustered together, and have a high degree of sequence similarity (94-80% among mammals; 94-75% overall). Frog and fish protein sequences have an intermediate level of similarity

(70-75% and 61-66%, respectively) compared with those of mammalian proteins, whereas Kidins220/ARMS amino acid sequences in nematoda, tunicata and cnidaria are considerably different from those in the other groups (Fig. 2A). Another phylogenetic cluster of Kidins220/ARMS homologues is represented by insects, whose protein sequences are more similar to each other than to any other organism. With the exception of the *D. melanogaster* Kidins220/ARMS sequence (which has an additional N-terminal extension) and that of *Bombus terrestris* (for which an N-terminal extension is also predicted), the N-terminal region of Kidins220/ARMS is highly conserved, whereas its C-terminal part is more divergent (Fig. 2B). On the basis of this analysis, it is possible that cytoskeletal remodelling, which is the main function associated with the N-terminus (Higuero et al., 2010; Neubrand et al., 2010; Park et al., 2010), is the most 'ancient' function of Kidins220/ARMS. This role has been maintained through evolution in organisms such as *D. melanogaster* and *C. elegans*, for which a canonical neurotrophin pathway has not yet been identified. As Kidins220/ARMS is present in cells of the immune system (Riol-Blanco et al., 2004; Ni et al., 2010; Jean-Mairet et al., 2011; Ni et al., 2011) and it is likely to be expressed in the cardiovascular system – hypothesised on the basis of functional data (Cesca et al., 2011; Cesca et al., 2012) – the C- and N-terminal parts of Kidins220/ARMS might have diverged, reflecting the different specialisation of tissues and organs in the various phylogenetic groups. Interestingly, the ephrin–Eph and VEGF–VEGFR pathways are more conserved in evolution than the neurotrophin-Trk system, and have also been identified in invertebrates (Drescher, 2002; Shibuya, 2002; Seipel et al., 2004; Mellott and Burke, 2008). Therefore, the neurotrophic function of Kidins220/ARMS might be a feature in organisms with a more complex nervous system, whereas in lower organisms, Kidins220/ARMS might contribute to the development of other tissues by modulating ephrin–Eph and VEGF–VEGFR pathways.

Kidins220/ARMS and neurotrophin signalling

As previously mentioned, Kidins220/ARMS interacts with Trk receptors (Arevalo et al., 2004), forming a ternary complex with p75[NTR] (Chang et al., 2004). The interaction between Kidins220/ARMS and TrkA is mediated by the fourth transmembrane

Table 1. Kidins220/ARMS binding partners

| Binding partner	Kidins220/ARMS binding site	References
AMPAR–GluA1	Transmembrane domains	(Arevalo et al., 2010)
α-syntrophin	PDZ-binding motif	(Luo et al., 2005)
CrkL	Proline-rich domain	(Arevalo et al., 2006)
EphA4	n.d.	(Luo et al., 2005)
Kinesin 1	KIM motif	(Bracale et al., 2007)
MAP1a, MAP1b, MAP2	Residues 760–1762	(Higuero et al., 2010)
NMDA receptor	n.d.	(Lopez-Menendez et al., 2009)
p75[NTR]	Residues 1512–1762	(Kong et al., 2001)
PDZ–GEF1	Indirect binding through S-SCAM	(Hisata et al., 2007)
PKD	n.d.	(Iglesias et al., 2000)
SCG10	Ankyrin repeats	(Higuero et al., 2010)
SCLIP	Ankyrin repeats	(Higuero et al., 2010)
Septin 5	Residues 1603–1715	(Park et al., 2010)
S-SCAM	PDZ-binding motif	(Hisata et al., 2007)
Trio, kalirin	Ankyrin repeats	(Neubrand et al., 2010)
TrkA, TrkB, TrkC	Transmembrane domain	(Kong et al., 2001; (Arevalo et al., 2004)
VEGFR2, VEGFR3	n.d.	(Cesca et al., 2012)
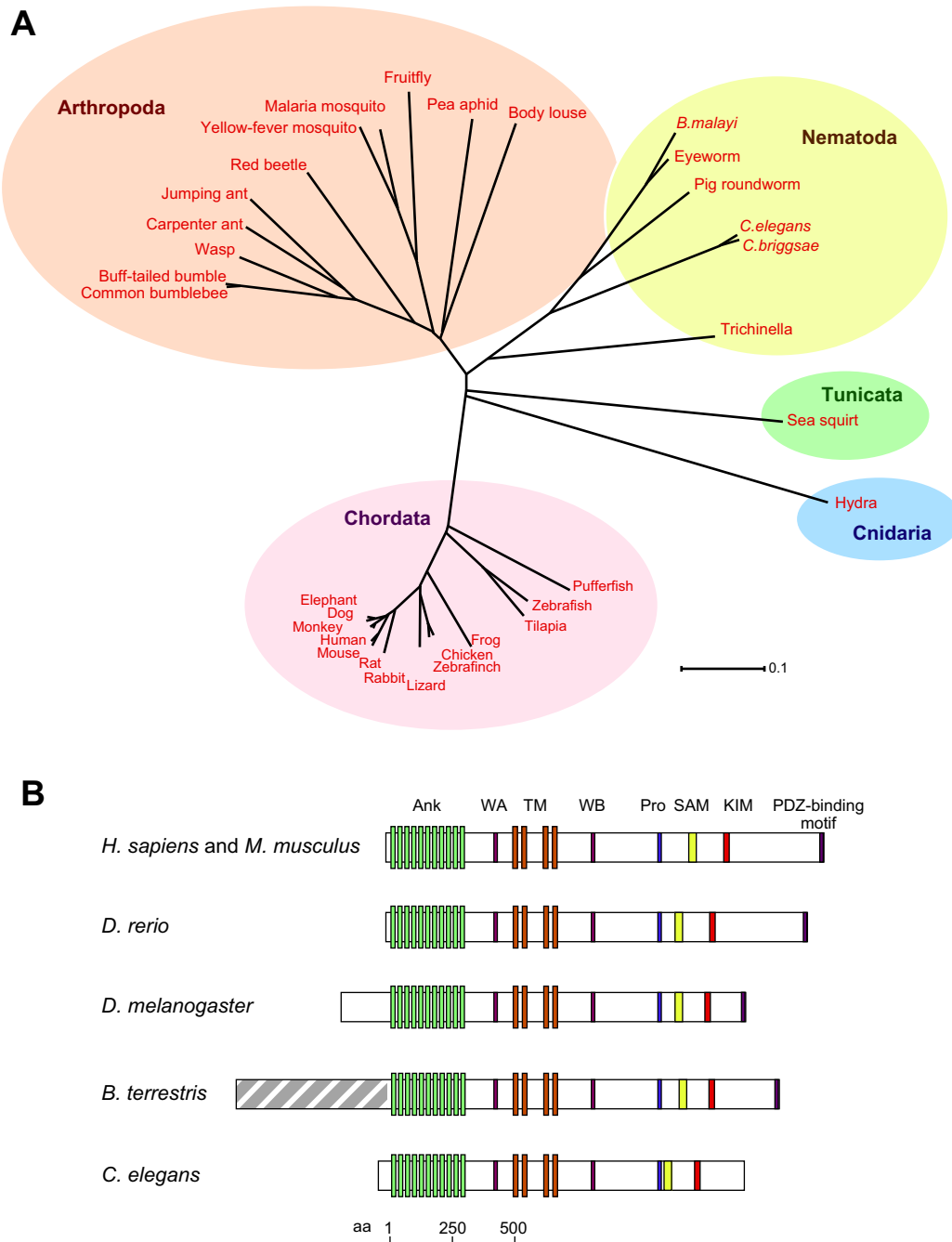
Fig. 2. Kidins220/ARMS in evolution. (**A**) Dendrogram of Kidins220/ARMS orthologues. The branch lengths are proportional to the amount of inferred evolutionary change between sequences. GenBank accession numbers are listed in Table 2. (**B**) Schematic of Kidins220/ARMS domain structure in the indicated species. Alternative splicing may occur in the C-terminal region between the KIM motif and the PDZ-binding domain (Iglesias et al., 2000). The shaded grey box in the *B. terrestris* sequence indicates a predicted N-terminal extension. Ank, ankyrin repeats; WA, Walker A motif; WB, Walker B motif; TM, transmembrane regions; Pro, proline-rich domain.

domain of Kidins220/ARMS and the transmembrane domain of TrkA (Arevalo et al., 2004) (Fig. 1), whereas the interaction with p75[NTR] involves the last 250 amino acids of Kidins220/ARMS (Kong et al., 2001) and the p75[NTR] intracellular domain (residues 327–342) (Chang et al., 2004). The binding of Trk receptors and p75[NTR] to Kidins220/ARMS is differentially modulated by neurotrophins. Formation of a Kidins220–TrkA complex is NGF-dependent and persists for up to 25 hours following

stimulation with NGF (Kong et al., 2001). The assembly of the ternary complex between Kidins220/ARMS, TrkA and p75[NTR] is however independent of NGF (Chang et al., 2004). Interestingly, increased levels of Kidins220/ARMS reduce the binding of TrkA to p75[NTR], suggesting that Kidins220/ARMS regulates the formation of receptor complexes that display different neurotrophin-binding affinities (Chang et al., 2004). In addition, Kidins220/ARMS selectively mediates the sustained

Table 2. Kidins220/ARMS orthologues and their GenBank accession numbers

Organism	Common name	GenBank accession number
Acyrthosiphon pisum	Pea aphid	XP_001943427
Anolis carolinensis	Lizard	XP_003215436
Anopheles gambiae	Malaria mosquito	XP_320386
Ascaris suum	Pig roundworm	ADY40531
Bombus impatiens	Common bumblebee	XP_003493060
Bombus terrestris	Buff-tailed bumble	XP_003400873
Brugia malayi	Round worm	XP_001895979
Caenorhabditis briggsae	Worm	XP_002633264
Caenorhabditis elegans	Worm	CAA92996
Camponotus floridanus	Carpenter ant	EFN63057
Canis lupus familiaris	Dog	XP_532865
Culex quinquefasciatus	Yellow-fever mosquito	XP_001843847
Danio rerio	Zebrafish	NP_956276
Drosophila melanogaster	Fruitfly	NP_611574
Gallus gallus	Chicken	XP_419939
Harpegnathos saltator	Jumping ant	EFN89445
Homo sapiens	Human	NP_065789
Hydra magnipapillata	Hydra	XP_002154747
Loa loa	Eye worm	XP_003141375
Loxodonta africana	Elephant	XP_003411847
Macaca mulatta	Monkey	XP_001083478
Mus musculus	Mouse	NP_001074847
Nasonia vitripennis	Wasp	XP_003426415
Oikopleura dioica	Sea squirt	CBY24367
Oreochromis niloticus	Tilapia	XP_003446685
Oryctolagus cuniculus	Rabbit	XP_002722525
Pediculus humanus corporis	Body louse	XP_00242719
Rattus norvegicus	Rat	NP_446247
Taeniopygia guttata	Zebra finch	XP_002197621
Tetraodon nigroviridis	Pufferfish	CAG10502
Tribolium castaneum	Red beetle	XP_001811729
Trichinella spiralis	Pork worm	XP_003380555
Xenopus tropicalis	Frog	NP_001120159

activation of MAPK signalling, without affecting the fast response to neurotrophins or the response to other growth factors, such as epidermal growth factor (EGF) (Kong et al., 2001; Arevalo et al., 2004).

Kidins220/ARMS is phosphorylated on tyrosine residues in response to NGF and BDNF, the time course of which follows the kinetics of Trk autophosphorylation and therefore suggests that this protein is a Trk receptor substrate (Kong et al., 2001). In addition, tyrosine phosphorylation of Kidins220/ARMS occurs simultaneously with that of Shc and PLCγ, indicating that this protein is amongst the first to be activated in response to NGF (Arevalo et al., 2004). The adaptor protein CrkL constitutively binds the second poly-proline stretch of Kidins220/ARMS through its SH3 domain (Arevalo et al., 2006). Upon treating cells with NGF, Kidins220/ARMS is phosphorylated at tyrosine 1096, causing a conformational change in the CrkL–Kidins220/ARMS complex. This allows the recruitment of downstream modulators of the MAPK pathway, such as C3G and Rap1 (Arevalo et al., 2006), and determines its sustained activation, which occurs mainly at late endosomes (Hisata et al., 2007). This effect is highly specific, as perturbing Kidins220/ARMS function by using RNA interference (RNAi) or dominant–negative Kidins220/ARMS constructs does not affect the transient MAPK activation triggered by EGF and the initial steps of MAPK signalling, which are Ras- or Akt-dependent (Arevalo et al., 2004). Impairment of BDNF-induced MAPK activation has

also been demonstrated in Kidins220/ARMS-deficient neurons (Cesca et al., 2012). Among the transcription factors activated by the MAPK pathway, Kidins220/ARMS promotes nuclear factor-kappa B (NF-κB) signalling when cells are treated with BDNF, mediating neuronal survival (Sniderhan et al., 2008). In support of these findings, Kidins220/ARMS$^{-/-}$ embryos show widespread cell death in the central nervous system (CNS) and peripheral nervous system (PNS) and die at birth (Cesca et al., 2011; Cesca et al., 2012). Remarkably, Kidins220/ARMS is one of the few proteins that is selectively required for the sustained activation of MAPK signalling, whereas most of the other factors act in both transient and sustained signalling.

Because of the role Kidins220/ARMS has in survival pathways such as MAPK signalling, it is recognised as a potential oncogene. Accordingly, Kidins220/ARMS prevents stress-induced apoptosis in melanoma cells and contributes to tumour progression (Liao et al., 2007; Liao et al., 2011).

Intracellular trafficking of Kidins220/ARMS

Intracellular traffic of Kidins220/ARMS is mediated through a direct binding of KIM to KLC-1 and KLC-2, and is important in ensuring a correct response to neurotrophic stimuli in the neuronal model cell line PC12 (Bracale et al., 2007). The KIM motif of Kidins220/ARMS does not bear sequence similarities with other KLC-binding proteins (Bracale et al., 2007; Dodding et al., 2011). Similarly, the part of KLC that interacts with KIM has so far not been implicated in cargo recognition, suggesting that – through its C-terminal region – KLC recruits other proteins, such as 14-3-3 protein (Ichimura et al., 2002) or Jun N-terminal kinase (JNK)-interacting proteins (JIPs) (Verhey et al., 2001). Furthermore, overexpression of Kidins220/ARMS does not interfere with the trafficking of other kinesin-1 cargoes (Bracale et al., 2007; Hammond et al., 2008). The Kidins220/ARMS–kinesin-1 complex might, therefore, constitute a modular scaffold for the assembly of larger protein complexes, in which single components associate with KLC as well as with the other domains of Kidins220/ARMS. Kidins220/ARMS might link motor proteins to inactive signalling complexes in order to mediate their targeting to specific domains of the plasma membrane. Once these complexes have been delivered to their final destination, they would become activated upon exposure to trophic stimuli.

The trafficking of Kidins220/ARMS to the plasma membrane relies on PKD activity (Sanchez-Ruiloba et al., 2006). PKD is a serine/threonine kinase involved in several cellular processes, such as cell proliferation and Golgi-complex trafficking (Van Lint et al., 2002). Kidins220/ARMS constitutively interacts with PKD and is phosphorylated by this kinase on serine 919 upon stimulation with phorbol ester (Iglesias et al., 2000). Kidins220/ARMS associates with membrane microdomains at the leading edge of motile immature dendritic cells (Riol-Blanco et al., 2004), of PC12 cells and of primary cortical neurons (Cabrera-Poch et al., 2004). This lipid-microdomain-associated pool of Kidins220/ARMS colocalises with PKD. In addition, Kidins220/ARMS and PKD are both present in the trans-Golgi network (TGN). The expression of a kinase-dead form of PKD alters the distribution of Kidins220/ARMS, causing its accumulation in intracellular structures that contain TGN markers. PKD activity controls Kidins220/ARMS trafficking to the plasma membrane through the phosphorylation-dependent recruitment of PDZ proteins at the TGN (Sanchez-Ruiloba et al., 2006). Therefore,

the interaction with PKD could regulate the formation of signalling platforms that contain Kidins220/ARMS and one or more membrane receptors.

Kidins220/ARMS regulates cytoskeletal remodelling and neuronal differentiation

The function of neurons greatly depends on their highly polarised morphology, which is established during development (da Silva and Dotti, 2002). Neurotrophins and other growth factors induce rearrangements of the cytoskeleton at growth cones and changes in gene expression (Huber et al., 2003), which need to be highly coordinated. Kidins220/ARMS is ideally suited to fulfil this role, because it is implicated in neurotrophin signalling and interacts with cytoskeletal components (Higuero et al., 2010; Neubrand et al., 2010; Park et al., 2010). Neurite outgrowth requires the formation of F-actin (Huber et al., 2003), and Kidins220/ARMS colocalises with F-actin in NGF-differentiated PC12 cells (Neubrand et al., 2010; Park et al., 2010) and hippocampal neurons (Higuero et al., 2010). Interestingly, the amount of F-actin at growth cones correlates with the amount of Kidins220/ARMS present at these sites (Higuero et al., 2010), indicating the importance of Kidins220/ARMS in cytoskeletal remodelling in developing neurons.

Park and colleagues recently characterised an interaction between Kidins220/ARMS and septin 5 (Park et al., 2010), a protein involved in cytoskeletal organisation and membrane tubulation (Tanaka-Takiguchi et al., 2009). Independently, we reported that Kidins220/ARMS binds and activates Trio (Neubrand et al., 2010), a RhoGEF that promotes neurite outgrowth through cytoskeletal remodelling (Dickson, 2001; Estrach et al., 2002; Govek et al., 2005). In NGF-stimulated PC12 cells, this characteristic of Trio has been linked to its first GEF domain, which activates the small GTPases Rac1 and RhoG (Bateman and Van Vactor, 2001; Estrach et al., 2002). This activity of the GEF domain is regulated by the flanking SH3 and spectrin domains of Trio. Crucially, Kidins220/ARMS binds to the latter region through its N-terminal ankyrin repeats (Neubrand et al., 2010). This interaction is important for the function of Trio, as overexpression of this domain causes widespread activation of Rac1. Because a localised activation of Rac1 at neurite tips is necessary for neurite extension (Aoki et al., 2004), the overexpression of the ankyrin repeats inhibits neurite outgrowth in PC12 cells and hippocampal neurons (Neubrand et al., 2010).

In addition to the actin cytoskeleton, Kidins220/ARMS interacts with microtubules by binding tubulin, the microtubule-associated proteins 1a, 1b and 2 (MAP1a, MAP1b and MAP2, respectively), and the stathmin family members SCG10 and SCLIP (also known as STMN2 and STMN3, respectively) (Higuero et al., 2010). These factors have a well-established role in neuronal morphogenesis (Poulain and Sobel, 2009) and their ability to modulate microtubule dynamics is phosphorylation dependent (Owen and Gordon-Weeks, 2003). In this context, Higuero and colleagues found a reduction in the phosphorylation of stathmin and MAP1b in Kidins220/ARMS knockdown neurons (Higuero et al., 2010). Interestingly, downregulation of Kidins220/ARMS in young hippocampal neurons favours the formation of multiple axon-like processes, whereas its knockdown in cells at later stages of differentiation leads to an aberrant dendritic arbour (Higuero et al., 2010). These results have been confirmed in Kidins220/ARMS$^{-/-}$ neurons, in

which longer axons and a simplified dendritic network were detected when compared with wild-type cells (Cesca et al., 2012).

In summary, Kidins220/ARMS controls axonal and dendritic maturation by directly modulating cytoskeletal dynamics and, in parallel, by inducing changes in sustained MAPK-dependent gene expression.

Effects of Kidins220/ARMS on neuronal activity

Neurotrophins are required for synaptogenesis and neuronal maturation (Martinez et al., 1998; Poo, 2001). Interestingly, the expression levels of Kidins220/ARMS are highly regulated during these processes (Cortes et al., 2007; Higuero et al., 2010). In hippocampal neurons, Kidins220/ARMS is more abundant during early stages of differentiation compared with later stages, when more synapses are present and neuronal activity is higher (Cortes et al., 2007; Higuero et al., 2010).

These findings support recent results suggesting that Kidins220/ARMS expression negatively regulates the membrane levels of the GluA1 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor (Arevalo et al., 2010). During neuronal development, this receptor is targeted to the cell surface to create a mature glutamatergic synapse (Hall and Ghosh, 2008). In the adult brain, GluA2 is the main AMPA receptor subunit, and the incorporation of the GluA1 subunit results in the formation of Ca^{2+}-permeable AMPA receptors that lack GluA2 (Bassani et al., 2009), which are crucial in establishing and maintaining synaptic plasticity (Man, 2011). Downregulation of Kidins220/ARMS by using RNAi or in Kidins220/ARMS$^{+/-}$ mice leads to an increase of GluA1 at the plasma membrane, which can be also detected as a rise in AMPA-receptor-mediated currents (Arevalo et al., 2010). In parallel, reduced levels of Kidins220/ARMS determine an increase in phosphorylation of GluA1 at Serine 831, which is associated with an enhanced receptor conductance (Benke et al., 1998; Derkach et al., 1999). Interestingly, GluA1 but not GluA2 co-immunoprecipitates with Kidins220/ARMS (Arevalo et al., 2010). These results suggest that, during development, in regions characterised by high levels of Kidins220/ARMS, GluA1-containing AMPA receptors are retained intracellularly through an interaction with Kidins220/ARMS. When neurons mature and synapses are formed, Kidins220/ARMS levels decrease, allowing for the surface expression of GluA1 and the establishment of synaptic strength. The GluA1-specific interaction of Kidins220/ARMS therefore suggests that this protein indirectly modulates Ca^{2+} homeostasis at the nerve terminal, and has a role in synaptic plasticity.

Kidins220/ARMS levels correlate with the activity of the neuronal network. In mature neuronal cultures, Kidins220/ARMS also associates with NMDA receptors (Lopez-Menendez et al., 2009). Upon overstimulation of the NMDA receptor, for example during excitotoxicity or when neurons are depolarised, activity-dependent Ca^{2+} influx through NMDA receptors leads to a decrease in Kidins220/ARMS levels owing to transcriptional downregulation (Lopez-Menendez et al., 2009) and protein cleavage by calpain (Lopez-Menendez et al., 2009; Wu et al., 2010). Because Kidins220/ARMS knockdown causes a decrease in the amount of phosphorylated MAPK (Lopez-Menendez et al., 2009), a reduction in the expression of Kidins220/ARMS might contribute to neuronal death through a decrease in MAPK signalling. Accordingly, in an animal model of cerebral ischemia, Kidins220/ARMS levels correlate with the extent of neuronal cell

death, which was attributed to excitotoxic NMDA-receptor activation (Lopez-Menendez et al., 2009). Altogether, these findings indicate that the amount of Kidins220/ARMS is tightly controlled and has a fundamental role in neuronal survival, both under basal and excitotoxic conditions. In addition to sites of calpain cleavage (Lopez-Menendez et al., 2009; Wu et al., 2010), sites of caspase-3-dependent cleavage (Ju et al., 2007) and of ubiquitylation (Kim et al., 2011) are present in the Kidins220/ARMS sequence. Further studies are therefore needed for a better understanding of the molecular mechanisms that regulate the turnover of Kidins220/ARMS.

Both excitatory and inhibitory circuits are influenced by Kidins220/ARMS. A decrease of Kidins220/ARMS in hippocampal neurons results in a lesser release of γ-aminobutyric acid (GABA), whereas overexpression of Kidins220/ARMS has the opposite effect, probably because of a mechanism that occurs at the presynaptic terminal (Sutachan et al., 2010). Our recent work, using cultured neurons from Kidins220/ARMS$^{-/-}$ mouse embryos, indicates that Kidins220/ARMS regulates the recovery of synaptic strength at inhibitory GABAergic synapses, whereas inhibitory basal transmission is not affected (Scholz-Starke et al., 2012). These findings are in line with previous data that show a reciprocal relationship between neuronal activity and the level of Kidins220/ARMS (Cortes et al., 2007). Interestingly, incubation of hippocampal neurons with either BDNF or the neuronal-activity-modulating tetrodotoxin causes an increase of Kidins220/ARMS expression, but combination of these treatments does not have an additive effect (Cortes et al., 2007). This observation suggests that neurotrophin- or activity-dependent changes control Kidins220/ARMS levels by acting on the same pathway. The involvement of Kidins220/ARMS in neurotrophin-dependent synaptic plasticity is further confirmed by the finding that BDNF-induced potentiation of excitatory postsynaptic currents is impaired in Kidins220/ARMS$^{-/-}$ neurons (Cesca et al., 2012). Altogether, these results suggest that Kidins220/ARMS functions as a neuronal maturation and activity sensor.

Most of these data were initially obtained by acute down- or upregulation of Kidins220/ARMS, and have subsequently been confirmed using Kidins220/ARMS$^{+/-}$ mice, which express 30–40% less protein than wild-type animals. In this mouse strain, both basal synaptic neurotransmission and long-term potentiation (LTP) are increased (Wu et al., 2009; Wu et al., 2010). In addition, they show defects in spatial memory formation (Duffy et al., 2011), a process in which a correct balance between LTP and long-term depression (LTD) is paramount (Kemp and Manahan-Vaughan, 2007; Ge et al., 2010). Because homozygous Kidins220/ARMS$^{-/-}$ embryos die at birth, future analysis of conditional Kidins220/ARMS$^{-/-}$ mouse lines will help to further our understanding on the role of this protein in synaptic plasticity and higher brain functions.

Neuronal activity also mediates structural modifications that are important for development of the CNS and for synaptic plasticity. BDNF is an important activity-dependent factor, which induces dendritic growth and controls dendritic spine morphogenesis (Cohen-Cory and Fraser, 1995; McAllister et al., 1995; Horch and Katz, 2002; Liu et al., 2007). Kidins220/ARMS$^{-/-}$ embryos and adult Kidins220/ARMS$^{+/-}$ mice display defects in dendritic growth and branching (Wu et al., 2009; Cesca et al., 2012), indicating that Kidins220/ARMS is important in BDNF-induced dendritic development. Dendritic branching correlates with the stabilisation of the synapse, which can be

assessed by measuring dendritic spine turnover. Indeed, spine stability is reduced in Kidins220/ARMS$^{+/-}$ mice (Wu et al., 2009), suggesting a role for Kidins220/ARMS in cytoskeletal remodelling events that underly the homeostatic control of these postsynaptic structures. In support of this idea, Kidins220/ARMS interacts with kalirin (Neubrand et al., 2010), a RhoGEF that controls the signalling events downstream of EphB, NMDA and AMPA receptors, which modulate the formation of dendritic spines (Penzes and Jones, 2008).

Kidins220/ARMS at the crossroad of several signalling streams

Kidins220/ARMS is not only involved in Trk, NMDA and AMPA receptor signalling, but it is also a downstream target of ephrins (Kong et al., 2001; Luo et al., 2005) and interacts with VEGFR (Cesca et al., 2012). Through its interaction with VEGFR, Kidins220/ARMS might have a role in vascular development, connecting neurotrophins with VEGF signalling. Indeed, Kidins220/ARMS$^{-/-}$ embryos reveal an abnormal vascular pattern in the brain (Cesca et al., 2012), similar to that observed in mice lacking neuropilin-1, a co-receptor of VEGFR (Gu et al., 2003). Additionally, Kidins220/ARMS is phosphorylated when cells that express EphB2 are stimulated with ephrin-B2 (Kong et al., 2001). Kidins220/ARMS also enhances EphA4 signalling, which is triggered by ephrin-A1 during the formation of the neuromuscular junction through its binding to α-syntrophin. Moreover, Kidins220/ARMS co-immunoprecipitates with and is phosphorylated by the EphA4 receptor (Luo et al., 2005).

TrkB, EphA4, EphB1, EphB2, EphB3, NMDA and AMPA receptors are all implicated in synaptogenesis and dendritic spine maturation (Constantine-Paton and Cline, 1998; Poo, 2001; Klein, 2009; Lai and Ip, 2009; McKinney, 2010). Interestingly, these receptors display a substantial crosstalk among each other; the NMDA receptor is phosphorylated upon BDNF stimulation (Lin et al., 1998) and the EphB extracellular domain interacts directly with the NMDA receptor (Dalva et al., 2000; Henderson et al., 2001). In addition, ephrin-B-mediated activation of EphB leads to NMDA-receptor-dependent Ca^{2+} influx (Takasu et al., 2002), which might influence the level of Kidins220/ARMS protein synthesis and its downstream signalling. Altogether, these data suggest that Kidins220/ARMS controls synaptic formation and stability by acting as a common downstream target of TrkB, NMDA, AMPA and EphB receptors. Fig. 3 summarises the present knowledge regarding the function of Kidins220/ARMS at synapses, both in the presynaptic compartment and in dendritic spines. Future studies aimed at increasing our understanding of these interactions are likely to reveal new aspects of the molecular mechanisms underlying synapse formation.

Future perspectives

Kidins220/ARMS orchestrates different functions in the nervous system as well as in other tissues. In addition to the neuronal phenotypes observed in the CNS and PNS, Kidins220/ARMS$^{-/-}$ embryos show cardiac malformations and severe defects in vascular development (Cesca et al., 2011; Cesca et al., 2012). Several reports also indicate a role for Kidins220/ARMS in the immune system (Riol-Blanco et al., 2004; Ni et al., 2010; Jean-Mairet et al., 2011; Ni et al., 2011). With full and conditional knockout mouse lines to hand, it will now be possible to carry out a functional analysis of this versatile protein in tissues other than
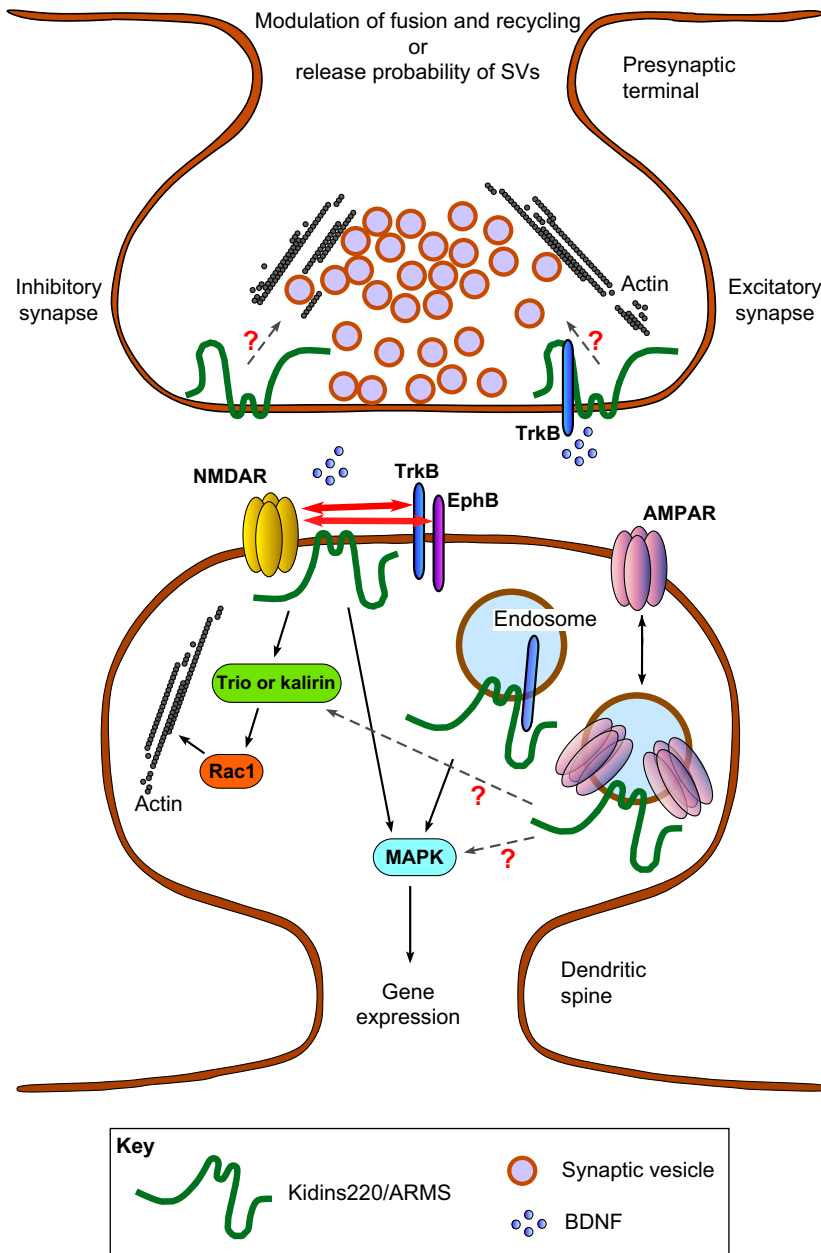
Fig. 3. Role of Kidins220/ARMS at synapses. At excitatory synapses, Kidins220/ARMS mediates BDNF-induced potentiation, whereas at inhibitory synapses, it is involved in neurotrophin-independent short-term plasticity. In both cases, the observed cellular phenotypes can be explained by alterations of synaptic vesicle fusion and recycling, or changes in the release probabilty. The precise molecular mechanisms at the basis of this regulation are presently unclear (red question marks). In dendritic spines, during synapse formation, NMDA, Trk and Eph receptors undergo substantial crosstalk with each other (red arrows), with Kidins220/ARMS as a possible common downstream target. Kidins220/ARMS signals to the actin cytoskeleton via Rac1 through its interaction with Trio or kalirin. In parallel, Kidins220/ARMS activates neuronal survival and differentiation by the sustained MAPK pathway, which mainly takes place on endosomal compartments. Kidins220/ARMS also regulates the targeting of the GluA1 subunit of the AMPA receptor to the cell surface. However, when and how Kidins220/ARMS is internalised is presently unknown. Kidins220/ARMS might signal to Trio (or kalirin) and MAPK from an AMPA-receptor-containing endocytic compartment (dashed arrows), but this hypothesis requires further investigation (indicated by red question marks). AMPAR, AMPA receptor; NMDAR, NMDA receptor.

the nervous system. These tools will also allow the differentiation of cell-autonomous and non-autonomous roles of Kidins220/ARMS in vivo. For example, extensive cell death was reported in brains of Kidins220/ARMS$^{-/-}$ embryos, leading to abnormal ventricle enlargement (Cesca et al., 2011; Cesca et al., 2012). Ablation of Kidins220/ARMS only in the nervous system, however, does not yield the high level of cell death observed in Kidins220/ARMS$^{-/-}$ embryos (Cesca et al., 2012). Because the apoptotic regions in Kidins220/ARMS$^{-/-}$ brains correspond to some of the areas that display abnormal vascular patterning, defective vascularisation might contribute, at least in part, to the instances of neuronal death observed in these areas.

Like neurotrophins and their receptors, Kidins220/ARMS is involved in regulating the equilibrium between cell death and cell survival by affecting signalling pathways that act as principal

regulators of this process, such as the ERK pathway (Martin and Clark, 2007). Indeed, Trk receptors were originally identified as oncogenes (Martin-Zanca et al., 1986). It is therefore not surprising that Kidins220/ARMS was suggested to have a role as an oncogene and that it is overexpressed in melanoma, a skin cancer of neural crest origin (Liao et al., 2007; Liao et al. 2011) and possibly in other types of cancer. Understanding how to control the activity of Kidins220/ARMS during tumour progression, for example by specifically targeting its NTPase domain, represents a possible avenue for therapeutic intervention and an attractive means to study the balance between death and survival signals. The involvement of Kidins220/ARMS in the vascular development within specific areas of the brain is also very appealing, both in the context of cancer therapy and following ischemic insults, whereby a boost in neovascularisation

might be beneficial. Future research in these areas can reveal exciting new directions for a better understanding of signal integration at cellular and tissue levels, and might offer new translational opportunities in important fields of medicine.

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