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Article

2014

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How to cite

JACKSON, Catherine L, BOUVET, Samuel. Arfs at a glance. In: Journal of cell science, 2014, vol. 127, n° Pt 19, p. 4103–4109. doi: 10.1242/jcs.144899

This publication URL: <https://archive-ouverte.unige.ch/unige:74486>

Publication DOI: [10.1242/jcs.144899](https://doi.org/10.1242/jcs.144899)

CELL SCIENCE AT A GLANCE

Arfs at a Glance

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ABSTRACT

The Arf small G proteins regulate protein and lipid trafficking in eukaryotic cells through a regulated cycle of GTP binding and hydrolysis. In their GTP-bound form, Arf proteins recruit a specific set of protein effectors to the membrane surface. These effectors function in vesicle formation and tethering, non-vesicular lipid transport and cytoskeletal regulation. Beyond fundamental membrane trafficking roles, Arf proteins also regulate mitosis, plasma membrane signaling, ciliary trafficking and lipid droplet function. Tight spatial and temporal regulation of the relatively small number of Arf proteins is achieved by their guanine nucleotide-exchange factors (GEFs) and GTPase-activating proteins (GAPs),

which catalyze GTP binding and hydrolysis, respectively. A unifying function of Arf proteins, performed in conjunction with their regulators and effectors, is sensing, modulating and transporting the lipids that make up cellular membranes. In this Cell Science at a Glance article and the accompanying poster, we discuss the unique features of Arf small G proteins, their functions in vesicular and lipid trafficking in cells, and how these functions are modulated by their regulators, the GEFs and GAPs. We also discuss how these Arf functions are subverted by human pathogens and disease states.

KEY WORDS: Arf small GTP-binding protein, Golgi, Lipid transport, Membrane contact site, Plasma membrane, Vesicle trafficking

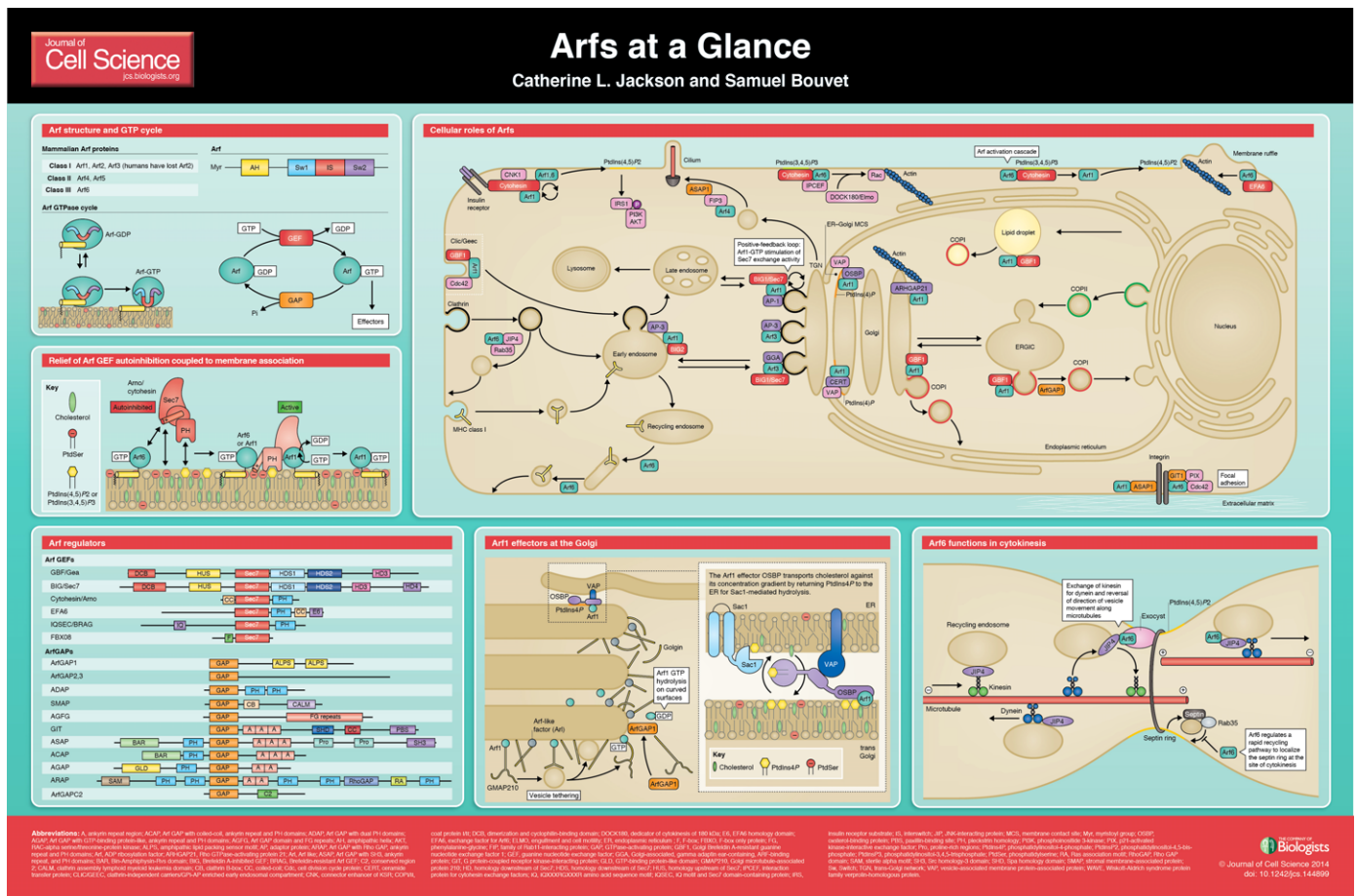
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Introduction

Members of the Arf family of small GTP-binding (G) proteins are key regulators of eukaryotic cell organization. Arf1 is the founding member of the family, and was originally identified as a protein factor required for the ADP-ribosylation of the adenylate cyclase activator Gs α by cholera toxin (Kahn and



Box 1. Regulation of trafficking to cilia by Arf family proteins

Cilia are vital for cell signaling and differentiation, and their impaired formation is responsible for numerous genetic disorders. Arf4 regulates trafficking to the cilium through interaction with cargo at the TGN (Deretic and Wang, 2012) (see main poster panel). Arf4 specifically recognizes the VxPx cytosolic targeting motif in retinal rhodopsin to facilitate its transport into the rod outer segment, a specialized cilium (Deretic et al., 2005). This ciliary targeting complex includes Rab11, FIP3 (a dual Arf and Rab11 effector) and ASAP1, an Arf GAP (Wang et al., 2012).

The importance of the larger Arf family, including the Arls, in intraflagellar transport and ciliogenesis is demonstrated by the crucial roles that Arl3, Arl6 and Arl13 have in these processes. Bardet-Biedl Syndrome is a disease caused by mutations in any one of 14 genes associated with ciliogenesis. Transport of membrane proteins into the cilium is driven by a complex of proteins, called the BBSome, whose subunits share similar structural folds to those found in COPI and adaptor protein (AP) complexes (Jin et al., 2010). Arl6 in its GTP-bound form is required to recruit the BBSome to the plasma membrane to drive cargo-sorting into cilia (Jin et al., 2010). Arl13 is mutated in patients with Joubert Syndrome, a cerebral disorder causing mental retardation, and functions in intraflagellar transport (Cevik et al., 2013). The retinitis pigmentosa 2 protein (RP2) is a GAP for Arl3 (Veltel et al., 2008), which functions in primary cilia to promote normal kidney and photoreceptor development (Schrick et al., 2006).

Gilman, 1986). There are three classes of Arf proteins in mammals, based largely on sequence homology – Class I (Arfs1–3), Class II (Arfs 4–5) and Class III (Arf6). Class I Arfs are highly conserved and are present in all eukaryotes, whereas the Class II Arfs arose during animal cell evolution, diverging from the Class I Arfs in the animal lineage after fungi separated, but before multicellular organisms arose (Manolea et al., 2010; Schlacht et al., 2013). Class III Arfs are ancient but, unlike Class I Arfs, are more divergent, especially in plants (Gebbie et al., 2005). The Arf proteins are part of a larger family that also includes the Arf-like (Arl) proteins (Gillingham and Munro, 2007) (Box 1).

The endoplasmic reticulum (ER) is the origin of organelles of the secretory pathway, including the Golgi. Arf1 plays a major role in this membrane system, along with Arf3, Arf4 and Arf5 (Donaldson and Jackson, 2011). Organelles of the endocytic pathway arise from the plasma membrane, beginning with the formation of endocytic vesicles from the plasma membrane (both clathrin-coated and non-clathrin types) (Grant and Donaldson, 2009). Arf6 functions in this plasma-membrane-endosomal membrane system (D'Souza-Schorey and Chavrier, 2006). These secretory and endosomal membrane systems intersect at the trans-Golgi network (TGN) and are maintained by recycling pathways (Saraste and Goud, 2007), in which Arf proteins play a major role.

In this Cell Science at a Glance and accompanying poster, we will describe the distinctive features of Arf small G proteins and important themes in their regulation. In addition to their fundamental roles in vesicular and non-vesicular lipid trafficking, we will highlight more specialized roles of Arf proteins, including functions in lipid droplet metabolism, the cytoskeleton, cell division and trafficking to cilia (Box 1).

Arf proteins and their regulators

A distinguishing feature of the Arf proteins is the presence of a myristoylated N-terminal amphipathic helix (see poster). Upon GTP binding, this helix inserts into the lipid bilayer, resulting in strong membrane association (Antonny et al., 1997). Hence, in addition to the changes in the switch regions, there is a second change in conformation in the GTP-bound form of Arfs, due to movement of the interswitch region into the hydrophobic pocket that harbors the amphipathic helix in the GDP-bound form (Goldberg, 1998; Liu et al., 2010; Pasqualato et al., 2001).

The Arf guanine nucleotide exchange factors (GEFs) catalyze GDP release from their substrate Arf, allowing GTP to bind. This activity is carried out by the evolutionarily conserved Sec7 domain (Chardin et al., 1996; Peyroche et al., 1996). The Arf GTPase activating proteins (GAPs) catalyze the hydrolysis of GTP on their substrate Arf through a conserved domain that contains a zinc finger (Cukierman et al., 1995). The last common ancestor of modern eukaryotic cells likely possessed only one Arf family member, in contrast to having nearly 20 Rab proteins (Koumandou et al., 2013). Multiple Arf GEFs and GAPs existed in this ancient eukaryote, supporting the idea that a key feature of Arf function is a single Arf protein participating in multiple GEF and GAP regulatory complexes (Koumandou et al., 2013; Schlacht et al., 2013).

Upon activation, Arf-GTP recruits specific proteins called effectors to the membrane surface. Although Arf effectors generally bind to the GTP-bound form of the protein, for at least a subset of Arfs (Arf4, Arf5 and Arf6), the GDP-bound form can also interact with a separate set of proteins on membranes, thereby increasing signaling capacity (Donaldson and Jackson, 2011). Classic effectors include coat complexes, lipid metabolic enzymes, lipid transfer proteins, membrane tethers, scaffold proteins and actin regulators.

Arf GEF regulation through cascades and positive-feedback loops

There are six subfamilies of Arf GEFs in eukaryotes (see poster). The GBF/Gea and BIG/Sec7 GEFs function sequentially in the secretory pathway, with GBF/Gea proteins acting at the early Golgi, and BIG/Sec7 proteins at the trans-Golgi and TGN (Donaldson and Jackson, 2011). The cytohesin/Arno, EFA6 and IQSEC/BRAG subfamilies function primarily in endosome-plasma-membrane trafficking pathways at the cell periphery, the latter two using Arf6 as a substrate (Casanova, 2007; Gillingham and Munro, 2007). The FBXO8 GEFs, restricted primarily to vertebrates, contain an F-box in addition to the Sec7 domain (Gillingham and Munro, 2007). Arf activation by GBF/Gea and BIG/Sec7 GEFs is inhibited by the drug brefeldin A, which traps a Sec7-domain-Arf-GDP complex (Mossessova et al., 2003; Peyroche et al., 1999; Renault et al., 2003).

Many GEFs exist in an autoinhibited state in the cytosol, with their activation coupled to membrane recruitment. At the plasma membrane, the Pleckstrin homology (PH) domains of the cytohesin/Arno GEFs interact with plasma-membrane-specific phosphoinositides – either phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P₂] or phosphatidylinositol (3,4,5)-trisphosphate [PtdIns(3,4,5)P₃] – and with the GTP-bound forms of either Arf6 (Cohen et al., 2007) or Arl4 (Hofmann et al., 2007; Li et al., 2007) (see poster). Elements that flank the PH domain of cytohesin block the catalytic site on the Sec7 domain (DiNitto et al., 2007). Interaction of the PH domain and these autoinhibitory regions with Arf6-GTP, interaction of the PH

domain with phosphoinositides and interaction of the polybasic region of cytohesin with acidic phospholipids all contribute to relieving autoinhibition (DiNitto et al., 2007; Malaby et al., 2013). Reconstitution of the cytohesin/Arno exchange reaction using an *in vitro* liposome assay revealed that the interaction of the PH domain with an activating Arf protein is an absolute requirement for the relief of autoinhibition (Stalder et al., 2011). This sequential activation of Arf proteins in a cascade ensures directionality in membrane maturation events.

Arf GEFs can engage in a positive-feedback loop whereby the product of the reaction stimulates exchange activity. Positive feedback has been demonstrated for cytohesin/Arno (Stalder et al., 2011) and the Golgi-localized Arf1 GEF Sec7 (Richardson et al., 2012). Cytohesins catalyze exchange on both Arf1 and Arf6 (Casanova, 2007; Macia et al., 2001), but the requirement for both a plasma-membrane-localized Arf and plasma-membrane-specific lipids ensures that cytohesins only become active at the plasma membrane. Cytohesin/Arno activation by positive feedback results in a remarkably high exchange rate ($k_{cat}/K_M \approx 10^6 \text{ M}^{-1}\text{s}^{-1}$) (Béraud-Dufour et al., 1998). To sustain this high level of activity, an abundant supply of Arf substrate is required. The fact that Arf1 is more abundant than Arf6 in cells might therefore explain why some cytohesin-mediated processes at the plasma membrane require both Arf1 and Arf6, such as membrane addition during phagocytosis (Beemiller et al., 2006) and insulin signaling (Lim et al., 2010).

In the case of Sec7, its HDS1 domain downstream of the catalytic Sec7 domain binds to membranes and to Arf1–GTP and, like the PH domain in the cytohesin GEFs, is responsible for mediating the relief of autoinhibition and positive feedback (Richardson et al., 2012). Sec7, the yeast homolog of BIG1 and BIG2, requires the HDS1–Arf1–GTP interaction for its Golgi localization (Richardson et al., 2012). By contrast, the HDS1 domain of GBF1 is a direct lipid-binding domain that does not require Arf1–GTP for membrane association, although this domain is important for the Golgi localization of GBF1 (Bouvet et al., 2013).

Arf GAPs and effector functions

There are 11 subfamilies of Arf GAPs, ten of which are found in humans (Schlacht et al., 2013) (see poster). A recent phylogenetic study has indicated that six Arf GAP families (ArfGAP1, ArfGAP2/3, SMAP, ACAP, AGFG and the newly identified ArfGAPC2 family) are ancient, whereas the ASAP, ARAP and GIT families arose more recently in evolution, being found only in animals. The lipid-binding PH, BAR and C2 domains of Arf GAP proteins are conserved across eukaryotes, and therefore were probably present in the primordial Arf GAPs, whereas other domains are restricted to specific lineages (Schlacht et al., 2013). These results suggest that interfacing with membrane lipids is a fundamental property of the Arf GAPs.

ArfGAP1 has two amphipathic lipid packing sensor (ALPS) motifs that mediate specific binding to highly curved membranes (Antony, 2011). Arf1–GTP recruits coat protein complex I (COPI) to membranes, which curves the membrane to form a vesicle. When curvature reaches a specific point, ArfGAP1 is recruited to hydrolyze the GTP on Arf1, the first step in the release of the coat from the vesicle membrane (Bigay et al., 2003). The peripheral Arf GAPs have numerous protein-interaction domains, and therefore are involved in complex signaling and cytoskeletal networks (Donaldson and Jackson, 2011; Inoue and Randazzo, 2007). In many cases, the

catalytically inactive form of an Arf GAP maintains functionality, and hence these multi-domain proteins have important roles as Arf effectors in addition to inactivating Arf proteins (Bharti et al., 2007; Donaldson and Jackson, 2011). Some peripheral Arf GAPs, including the ACAP and ASAP family members, contain a BAR domain, which both senses and induces membrane curvature (Gillingham and Munro, 2007; Nie et al., 2006). Others contain domains such as RhoGAP, ankyrin repeats and Src homology-3 (SH3) domains that are involved in actin cytoskeleton interaction and signaling networks. These Arf GAPs localize to focal adhesions, invadopodia and dorsal ruffles, where they perform important functions in normal cells, and are also required for invasion and metastasis of cancer cells (Randazzo et al., 2007; Sabe et al., 2006).

Arf effectors in vesicle trafficking

Arf1 and Arf6 both function in the recycling arm of bidirectional trafficking routes (see main poster panel). Anterograde trafficking through the secretory pathway begins with formation of COPII-coated vesicles from the ER (Lee et al., 2004). Arf1 recruits the COPI coat to membranes of the early secretory pathway, to recycle trafficking machinery and escaped ER-resident proteins from the Golgi back to the ER. Arf6 functions in multiple recycling routes after endocytic internalization from the plasma membrane. Together with its effector Jip4, Arf6 mediates rapid recycling back to the plasma membrane of components internalized in clathrin-coated vesicles (Montagnac et al., 2009). It also mediates a slower recycling of components internalized by clathrin-independent pathways (that internalize cargo such as MHC class I) at the level of the recycling endosome (Grant and Donaldson, 2009). Arf1, along with its GEF GBF1, are required for the ‘clathrin-independent carriers/GPI-AP-enriched early endosomal compartment’ (CLIC/GEEC) endocytic pathway (Howes et al., 2010).

The TGN is a major sorting station in the secretory pathway, where proteins destined for early or late endosomes, lysosomes or the plasma membrane are sorted into distinct classes of vesicles. Many of these vesicles are formed by Arf1–GTP-mediated recruitment of coats (including AP-1, GGA and AP-3) to membranes (Bonifacino and Glick, 2004). Recently, structural studies of Arf1–coat complexes have shown that Arf1 not only recruits but also mediates conformational changes of the coat during cargo binding (Ren et al., 2013; Yu et al., 2012).

Arf1 also recruits long coiled-coil proteins, the golgins, such as GMAP-210 (also known as TRIP11) to Golgi membranes, a function it shares with the Arl proteins (Munro, 2011). GMAP-210 associates with Golgi membranes through its C-terminal GRIP-related Arf-binding (GRAB) domain, which binds specifically to Arf1–GTP (Gillingham et al., 2004). The N-terminus of GMAP-210 contains an ALPS motif that binds to the highly curved membranes of early Golgi vesicles (Cardenas et al., 2009; Drin et al., 2008). ArfGAP1 is also recruited specifically to highly curved membranes through its ALPS motifs, and so will hydrolyze GTP on Arf1 only on curved surfaces, not on flat ones. In this way, a self-organizational module is established that will specifically tether a vesicle to a flat Golgi membrane in a dynamic manner (Drin et al., 2008). The perception of golgins as tentacles, having one end anchored to flat Golgi cisternae and the other extending out to capture vesicles by various mechanisms, has led to the proposal that golgins form a tentacular cytomatrix around Golgi membranes to facilitate vesicle flow to and through the Golgi (Munro, 2011).

Arf effectors in lipid trafficking

Membrane contact sites (MCS) play an important role in the itinerary of non-vesicular lipid movement among cellular organelles (Levine and Rabouille, 2005; Stefan et al., 2013; Voelker, 2003). At contact sites between the ER and the Golgi, Arf1 is required for the recruitment of several lipid transfer proteins, including FAPP2, CERT and OSBP, which transfer glucosylceramide, ceramide and sterols, respectively (see poster). All three possess a PH domain that requires both Arf1 and phosphatidylinositol-4-phosphate (PtdIns4P) in order to bind to trans-Golgi membranes (De Matteis and Godi, 2004). In addition, they have a motif that mediates binding to the ER-localized protein VAP (Lev, 2010; Levine and Loewen, 2006). These two localization regions of OSBP are sufficient to mediate contact between the ER and Golgi, and moreover, OSBP activity regulates this association (Mesmin et al., 2013). FAPP2-mediated delivery of glucosylceramide to the trans-Golgi has been shown to be dependent on Arf1 and also to be involved in vesicular trafficking from the Golgi to the plasma membrane (D'Angelo et al., 2007; D'Angelo et al., 2013). Hence, Arf1, by recruiting proteins that mediate the transfer of sphingolipid precursors and cholesterol, plays an important role in establishing the characteristic lipid environment of cellular membranes, an evolutionarily conserved feature of cellular organization (Bigay and Antonny, 2012).

All Arf proteins can both localize to membranes and stimulate the activity of phosphatidylinositol 4-phosphate 5-kinase (PIP5K) (Honda et al., 1999) and phospholipase D (PLD) (Cockcroft, 2009; Jenkins and Frohman, 2005), enzymes that regulate key structural and signaling lipids. PIP5K generates PtdIns(4,5) P_2 , which has many effectors, notably those involved in regulating the actin cytoskeleton and endocytosis at the plasma membrane (Vicinanza et al., 2008). In cells, it is primarily Arf6 that recruits PIP5K to the plasma membrane to generate PtdIns(4,5) P_2 , which, in turn, stimulates plasma membrane ruffling (Honda et al., 1999). Arf proteins are positive activators of the insulin signaling pathway through their activation of PtdIns(4,5) P_2 (Fuss et al., 2006; Hafner et al., 2006; Lim et al., 2010). At the Golgi, Arf1 recruits and stimulates the activity of phosphatidylinositol 4-kinase, forming PtdIns4P, an important regulator of sterol trafficking in cells (Mesmin et al., 2013).

Arf1 in lipid droplet function

Arf1, along with its GEF GBF1 and effector COPI, function in lipid droplet metabolism (Beller et al., 2008; Guo et al., 2008; Soni et al., 2009). Lipid droplets are well known for their function in the storage of energy in the form of triglycerides (Ducharme and Bickel, 2008; Londos et al., 2005). Their dynamic structure and integration with membrane trafficking pathways has revealed that they are in fact bona fide organelles (Walther and Farese, 2012). Arf1, GBF1 and COPI associate with lipid droplets and are required for the recruitment of a subset of lipid-droplet-associated proteins to the lipid droplet surface, including a triglyceride lipase (ATGL) and perilipin 2 (Soni et al., 2009). GBF1 itself is recruited to lipid droplets through its 'homology downstream of Sec7' (HDS)1 domain, which binds to lipid droplets in cells and *in vitro* (Bouvet et al., 2013). Arf1-GTP and COPI can function directly on the lipid droplet surface and have been shown to mediate the budding of 60–100-nm diameter droplets from an artificial droplet surface *in vitro* (Thiam et al., 2013). This mechanism is important for the regulation of the surface properties of lipid droplets during different stages of their metabolism in cells (Wilfling et al., 2014).

Arf regulation of the actin cytoskeleton

Arf proteins control the actin cytoskeleton through the production of PtdIns(4,5) P_2 , an important actin regulatory lipid, and through interaction with actin regulators, such as Rho family GTPases (Myers and Casanova, 2008). ARHGAP21 is an effector of Arf1 at the Golgi, and is also a GAP for Cdc42 (Dubois et al., 2005; Ménétrey et al., 2007). Arf GEFs (notably cytohesins and EFA6) and Arf GAPs also interact with Rho-family G proteins and other actin cytoskeleton regulators (Myers and Casanova, 2008; Randazzo et al., 2007). Arf6 activates Rac by recruiting the Rac GEF complex DOCK180/Elmo to the plasma membrane, a process that is mediated in part through the binding of cytohesin to the DOCK180 interactor IPCEF (Santy et al., 2005; White et al., 2010). In addition, Arf1 cooperates with Rac for efficient recruitment of the WASP family verprolin-homologous protein (WAVE) regulatory complex to the plasma membrane (Koronakis et al., 2011). A major function of the large multi-domain Arf GAPs is to coordinately regulate membrane and actin cytoskeleton remodeling through interactions with membranes and with regulators of the actin cytoskeleton (D'Souza-Schorey and Chavrier, 2006; Randazzo et al., 2007).

Arf function in mitosis

Golgi disassembly during mitosis requires the inactivation of Arf1, with constitutive Arf1 activity leading to defects in both chromosome segregation and ingression of the cleavage furrow during cytokinesis (Altan-Bonnet et al., 2003). Arf1 inactivation is mediated in part by phosphorylation of its GEF GBF1 by AMP-activated protein kinase (AMPK) (Mao et al., 2013) and cyclin-dependent kinase 1 (CDK1)-cyclin-B (Morohashi et al., 2010) during mitosis. Arf1-GTP mediates the recruitment of golgin160 to Golgi membranes, and golgin160, in turn, recruits cytoplasmic dynein to position the Golgi near the centrosome (Yadav et al., 2012). Owing to Arf1 inactivation in mitosis, the dynein-golgin160 complex is released from Golgi membranes, thus contributing to Golgi disassembly (Altan-Bonnet et al., 2003; Yadav et al., 2012).

Arf6 acts at multiple stages of cytokinesis to coordinate membrane and cytoskeletal functions (see poster). Arf6 and Rab35 are part of an inhibition cascade whereby EPI64B (also known as TBC1D10B), a GAP for Rab35, is an effector of active Arf6 (Chesneau et al., 2012). This cascade ensures the sequential action of Arf6 and Rab35 in a rapid endocytic recycling pathway that is required for the dynamic localization of septins to the intercellular bridge, which, in turn, promotes cleavage furrow ingression (Chesneau et al., 2012). Arf6 is also involved in membrane addition to the cleavage furrow, mediating vesicle targeting and directional movement of vesicles to and from the furrow (Montagnac et al., 2009). Arf6 localizes to the midbody during the late stages of abscission, through interaction with mitosis kinesin-like protein 1 (MKLP1). The Arf6-MKLP1 complex links the plasma membrane to the microtubules running through the midbody, a step required for cell separation (Makyio et al., 2012). These functions of Arf6 are probably not essential to cytokinesis in all cells, as Arf6-knockout mice are viable at birth (Suzuki et al., 2006) and a *Drosophila* Arf6^{-/-} mutant has cytokinesis defects only in spermatocytes (Dyer et al., 2007).

Arf proteins and their regulators in human disease

Genetic diseases caused by mutations in Arf proteins and their regulators have started to emerge. Mutations in the Arf1 GEF BIG2 have been linked to autosomal recessive periventricular

heterotopia (ARPH), a disorder that leads to severe malformation of the cerebral cortex (Sheen et al., 2004). Disease symptoms are a result of the failure of a specific class of neurons to migrate from their point of origin to the cerebral cortex, due to a defect in the adhesion properties of these neurons (Ferland et al., 2009; Sheen et al., 2004). The IQSEC/BRAG Arf GEFs are highly expressed in the postsynaptic density of the central nervous system (Casanova, 2007), and play important roles in signaling during synaptic transmission (Myers et al., 2012). IQSEC2/BRAG1 is mutated in X-linked nonsyndromic intellectual disability, a form of mental retardation (Shoubridge et al., 2010a; Shoubridge et al., 2010b).

Arf proteins and their regulators are hijacked by numerous bacterial and viral pathogens (Dautry-Varsat et al., 2005; Goody and Itzen, 2013; Hsu et al., 2010; Humphreys et al., 2013; Matto et al., 2011). *Legionella pneumophila* and *Rickettsia prowazekii* encode an Arf GEF (RalF, acquired through horizontal transfer from their eukaryotic hosts), which recruits and activates Arf1 at the vacuoles that support its replication (Amor et al., 2005; Nagai et al., 2002). The bacterial pathogen *Salmonella* induces macropinosomes to which Arf1 and Arf6 localize, acting in a cascade whereby Arf6 recruits cytohesin/Arno to activate Arf1, which, in turn, leads to the recruitment of the WAVE complex (Humphreys et al., 2013). A recent study has found a novel role for Arf4 in mediating a stress-induced signaling cascade that is used by bacterial pathogens (Reiling et al., 2013). GBF1 is required for the replication of numerous plus-strand RNA viruses, including enteroviruses, hepatitis C virus and coronaviruses (Belov et al., 2008; Goueslain et al., 2010; Lanke et al., 2009; Verheije et al., 2008). These viruses remodel the ER and early secretory pathway membranes to form replication complexes, the function of which requires GBF1 and its substrate Arf1 (Belov et al., 2005; Matto et al., 2011), in coordination with lipids such as PtdIns4P (Hsu et al., 2010; Zhang et al., 2012).

Conclusions

Arf proteins have well-studied roles in vesicular trafficking that they accomplish through membrane recruitment of coat proteins, membrane tethers and cytoskeletal regulators that orchestrate the formation and flow of vesicles in cells. More recently, novel functions for Arf proteins in the non-vesicular trafficking of lipids, in lipid signaling and in lipid metabolism have begun to emerge. These novel lipid trafficking functions provide new directions for understanding the roles of Arf proteins in diverse cellular processes that are important for cellular organization.

Competing interests

The authors declare no competing interests.

Funding

Work in the authors' laboratory was funded by grants from the Agence Nationale de la Recherche, the Fondation pour la Recherche Médicale and by the Centre National de la Recherche Scientifique.

Cell science at a glance

A high-resolution version of the poster is available for downloading in the online version of this article at jcs.biologists.org. Individual poster panels are available as JPEG files at <http://jcs.biologists.org/lookup/suppl/doi:10.1242/jcs.144899/-DC1>.

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