Consensus nomenclature for the human ArfGAP domain-containing proteins

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At the FASEB summer research conference on "Arf Family GTPases", held in Il Ciocco, Italy in June, 2007, it became evident to researchers that our understanding of the family of Arf GTPase activating proteins (ArfGAPs) has grown exponentially in recent years. A common nomenclature for these genes and proteins will facilitate discovery of biological functions and possible connections to pathogenesis. Nearly 100 researchers were contacted to generate a consensus nomenclature for human ArfGAPs. This article describes the resulting consensus nomenclature and provides a brief description of each of the 10 subfamilies of 31 human genes encoding proteins containing the ArfGAP domain.

Introduction

Regulatory GTPases act as molecular switches that can rapidly interconvert between two conformational states, depending on whether GTP or GDP is bound. The cellular actions of GTPases are typically initiated by GTP binding, promoted by guanine nucleotide exchange factors (GEFs), and terminated by GTP hydrolysis that is facilitated by GTPase-activating proteins (GAPs). Within the Ras superfamily (Wennerberg et al., 2005), comprised of >150 GTPases, each family (Ras, Rho, Rab, Arf, and Ran) uses distinct sets of GEFs and GAPs to regulate signaling. Though originally envisioned as simple "off switches" in Arf signaling, the ArfGAPs have also emerged as effectors and key components in the assembly of nanomachines with complex signaling potential (Gillingham and Munro, 2007; Inoue and Randazzo, 2007).

ArfGAPs are a family of proteins containing a characteristic module, the ArfGAP domain, which was first identified in rat ArfGAP1 as the domain responsible for stimulation of GTP hydrolysis on Arf1 (Cukierman et al., 1995). ArfGAP domains are ancient and highly conserved since the earliest eukaryotes. Five ArfGAPs have been identified in the yeast *Saccharomyces cerevisiae* and shown to display a combination of redundant and unique functions. Mammalian cells express an array of ArfGAPs ranging from relatively small proteins resembling those found in yeast to the large, multi-domain ArfGAPs that are proposed to function as scaffolds for cell signaling (Fig. 1 A).

Structure, mechanism, and specificity

ArfGAP domains are ~130 amino acids in length and were originally defined as the minimal fragment possessing ArfGAP activity (Cukierman et al., 1995). They contain a characteristic C_4-type zinc finger motif and a conserved arginine that is required for activity, within a particular spacing ($CX_2CX_{16}CX_2CX_4R$). The zinc finger has an architectural rather than catalytic role (Fig. 1 B) (Goldberg, 1999). The invariant arginine was proposed to serve in a catalytic "arginine finger" mechanism, similar to that found in GAPs for other GTPases, including Ras and Rho (Scheffzek et al., 1998), and is highly exposed to solvent in the crystal structure (Fig. 1 B). However, the potential for other binding partners (e.g., coatomer; Goldberg 1999) or other domains within some ArfGAPs (e.g., PH domains) serving supportive or regulatory roles in GAP-stimulated hydrolysis has also been demonstrated. For example, the ArfGAP activity of ASAP1 is dependent on the PH domain and is sensitive to $PI(4,5)P_2$, and that of GITs is stimulated by PIP_3.

ArfGAPs display various degrees of specificity for individual members of the Arf family both in vitro and in live cells. However, these data are not easy to interpret due to uncertainties

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Abbreviations used in this paper: ArfGAP, Arf GTPase activating protein; Arl, Arf-like; FG, phenylalanine-glycine; GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor.

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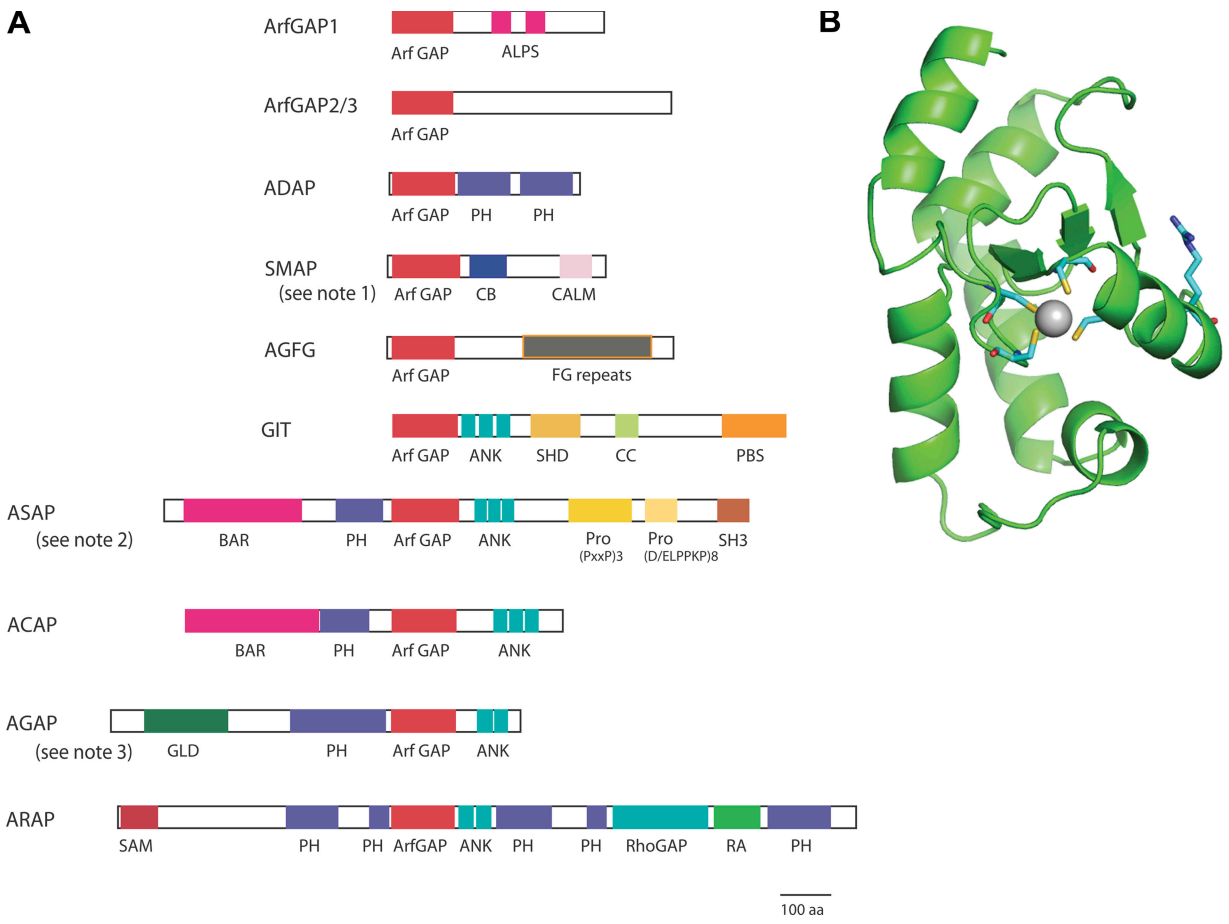

Figure 1. **Domain organization of human ArfGAP subfamilies and structure of the ArfGAP domain.** (A) Representative domain structures of each human ArfGAP subfamily are depicted and are drawn to scale. Abbreviations are: ALPS, ArfGAP1 lipid-packing sensor; ArfGAP, ArfGAP domain; ANK, ankyrin repeat; BAR, Bin/Amphiphysin/Rvs; CALM, CALM binding domain; CB, clathrin-box; CC, coiled-coil; FG repeats, multiple copies of the XXFG motif; GLD, GTP-binding protein-like domain; PBS, Paxillin binding site; PH, pleckstrin homology domain; Pro(PxxP)3, cluster of three Proline-rich (PxxP) motifs; Pro(D/ELPPKP)8, eight tandem Proline-rich (D/ELPPKP) motifs; RA, Ras association motif; RhoGAP, RhoGAP domain; SAM, sterile α-motif; SH3, Src homology 3 domain; SHD, Spa-homology domain. Notes: (1) SMAP2 has CALM BD, but SMAP1 does not. (2) ASAP1 contains the indicated Pro-rich domains; ASAP2 and ASAP3 lack the Pro (D/ELPPKP) repeat and ASAP3 does not have an SH3 domain. (3) AGAP2 has a splice variant with three N-terminal PxxP motifs, called PIKE-L. (B) The structure of the isolated ArfGAP domain of human ArfGAP1 (residues 6–120) is displayed with the backbone shown in green with secondary structures indicated. The side chains of only the conserved arginine (Arg50, on the right) and the four zinc finger cysteines (center; Cys22, 25, 42, and 45) are displayed along with the coordinated Zn2+ (gray sphere). This image was generated using PyMol.

in colocalization of the ArfGAP and Arfs in cells, incomplete knowledge of the importance of coregulators (lipids or other proteins), and because some ArfGAPs use their GAP domain to bind Arf without promoting GTP hydrolysis. For the most part (see below) ArfGAPs are active on one or more of the "true" Arfs (Arf1-6) but not on the Arf-like (Arl) or Sar proteins, which use distinct families of GAPs. Arf GAP activity has been demonstrated in vitro for at least one member of each subfamily, with the exception of the ADAPs, which appear to lack in vitro GAP activity. However, overexpression of ADAP1 reduces activated Arf6 (but not Arf1) levels, and diminishes cortical actin and stress fibers, consistent with function as an Arf6 GAP.

Although ArfGAPs had been thought to distinguish between Arfs and Arls, Gcs1p (a yeast orthologue of mammalian ArfGAP1) was reported to function as GAP for both yeast Arf1p and Arl1p (Liu et al., 2005). Conversely, Arl2 GAP isolated from bovine testis lacks the ArfGAP domain but exhibits GAP activity toward Arfs (Bowzard et al., 2007). The latter finding suggests that the "canonical" ArfGAPs, those containing the ArfGAP domain, may not represent the entire repertoire of proteins capable of stimulating GTP hydrolysis by Arf proteins.

Consensus nomenclature of the ArfGAP family of human genes and encoded proteins

Like most gene families today, gene/protein discovery and the accompanying nomenclature of ArfGAPs has come from a number of different laboratories and techniques and over a span of more than a decade. We have developed a consensus nomenclature for the human ArfGAPs that is based upon the phylogeny of the ArfGAP domains and the domain organization of the proteins, and updated or clarified the acronyms in use to more accurately describe the current understanding of each protein. Table I lists the consensus nomenclature for the human genes, previously published gene symbols and names, database identifiers, chromosome locations, and accession numbers. These gene names should also be used for the encoded proteins, with appropriate

Table I. **Consensus names for human ArfGAPs, with additional information**

Subfamily	New consensus gene symbols	Previous HGNC gene symbols	Literature or database aliases/synonyms				KIAA#	NCBI gene ID	Human gene location	Accession number (length)
			Name #1	Name #2	Name #3	Name #4				
ARFGAP1	ARFGAP1	ARFGAP1	ArfGAP1	Arf1GAP	Arf GAP	MGC39924		55738	20q13.33	NM_018209; NP_060679 (406aa)
ARFGAP2	ARFGAP2	ARFGAP2	ArfGAP2	ZNF289/Zfp289	FLJ14576	FLJ26000		84364	11p11.2-p11.12	NM_032389; NP_115765 (521aa)
	ARFGAP3	ARFGAP3	ArfGAP3	ArfGAP1				26286	22q13.2-q13.3	NM_014570; NP_055385 (516aa)
ADAP	ADAP1	CENTA1	Centaurin (alpha1)	PIPBP	p42IP4	GCS1L		11033	7p22.3	NM_006869; NP_006860 (374aa)
	ADAP2	CENTA2	Centaurin (beta)	Cent. Alpha2	cent-b	HSA272195		55803	17q11.2	NM_018404; NP_060874 (381aa)
SMAP	SMAP1	SMAP1	SMAP-1	FLJ13159	FLJ42245			60682	6q13	NM_001044305; NP_068759 (440aa)
	SMAP2	SMAP2	SMAP1L	RP1-228H13.3	SMAP2			64744	1p35.3-p34.1	NM_022733; NP_073570 (429aa)
AGFG	AGFG1	HRB	HRB1	RIP	HIV-1 Rev BP	RAB		3267	2q36.3	NM_004504; NP_004495 (562aa)
	AGFG2	HRBL	HRB2	RAB-R/HRB1	HIV-1 Rev BP-L			3268	7q22.1	NM_006076; NP_006067 (481aa)
GIT	GIT1	GIT1	Git1	Cat1	p95APP1			28964	17p11.2	NM_014030; NP_054749 (761aa)
	GIT2	GIT2	Git2	Cat2	p95APP2	p95PKL	KIAA0148	9815	12q24.1	NM_057169; NP_476510 (759aa)
ASAP	ASAP1	DDEF1	AMAP1	DEF1/DDEF1	PAG2/SHAG1	Cent. Beta4	KIAA1249	50807	8q24.1-q24.2	NM_018482; NP_060952 (1129aa)
	ASAP2	DDEF2	AMAP2	PAP/DDEF2	SHAG2/PAG3	Cent. Beta3	KIAA0400	8853	2p24	NM_003887: NP_003878 (1006aa)
	ASAP3	DDEFL1	DDEFL1	UPLC1	ACAP4	Cent. Beta6		55616	1p36.12	NM_017707; NP_060177 (903aa)
ACAP	ACAP1	CENTB1	ACAP1	Cent. Beta1			KIAA0050	9744	17p13.1	NM_014716; NP_055531 (740aa)
	ACAP2	CENTB2	ACAP2	Cent. Beta2			KIAA0041	23527	3q29	NM_012287; NP_036419 (778aa)
	ACAP3	CENTB5	ACAP3	Cent. Beta5			KIAA1716	116983	1p36	NM_030649; NP_085152 (759aa)
AGAP	AGAP1	CENTG2	AGAP1	Cent. Gamma2	GGAP1	MGC71657	KIAA1099	116987	2q37	NM_014914; NP_055729 (804aa)
	AGAP2	CENTG1	AGAP2	Cent. Gamma1	GGAP2/PIKE	FLJ16430	KIAA0167	116986	12q14.1	NM_014770; NP_055585 (836aa); AAM97540 (1192aa)
	AGAP3	CENTG3	AGAP3	Cent. Gamma3	MRIP1/CRAG	FLJ16146		116988	7q36.1	NM_031946; NP_114152 (911aa)
	AGAP4	CTGLF1	CTGLF1	Centaurin gamma-like family 1	MRIP2			119016	10q11.21	NM_133446; NP_597703 (663aa)
	AGAP5	CTGLF2	CTGLF2	Centaurin gamma-like family 2				729092	10q22.2	XM_001132588; XP_001132588 (686aa)
	AGAP6	CTGLF3	CTGLF3	Centaurin gamma-like family 3				414189	10q11.23	NM_001077665; NP_001071133 (686aa)
	AGAP7	CTGLF4	CTGLF4	Centaurin gamma-like family 4				653268	10q11.23	NM_001077685; NP_001071153 (663aa)
	AGAP8	CTGLF5	CTGLF5	Centaurin gamma-like family 5				728404	10q11.23	NM_001077686; NP_001071154 (663aa)
	AGAP9	CTGLF6	CTGLF6	Centaurin gamma-like family 6	FLJ00312			642517	10q11.22	NM_001077686 (663aa)
	AGAP10	CTGLF7	CTGLF7	Centaurin gamma-like family 7				728127	10q11.22	XR_015281 (655aa)
	AGAP11	KIAA1975		Similar to MRIP2			KIAA1975	119385	10q23.2	NP_597704 (550aa)
ARAP	ARAP1	CENTD2	ARAP1	Cent. Delta2			KIAA0782	116985	11q13.4	NM_001040118; NP_001035207 (1450aa)
	ARAP2	CENTD1	ARAP2	Cent. Delta1	FLJ13675	PARX	KIAA0580	116984	4p14	NM_015230; NP_056045 (1704aa)
	ARAP3	CENTD3	ARAP3	Cent. Delta3	FLJ21065	DRAG1		64411	5q31.3	NM_022481; NP_071926 (1544aa)

List of consensus acronyms: ArfGAP = ADP-ribosylation factor GTPase activating proteins. ACAP = ArfGAP with coiled-coil, ankyrin repeat, and PH domains. ADAP = ArfGAP with dual PH domains. AGAP = ArfGAP with GTPase domain, ankyrin repeat, and PH domain. AGFG = ArfGAP with FG repeats. ARAP = ArfGAP with Rho GAP domain, ankyrin repeats and PH domain. ASAP = ArfGAP with SH3 domain, ankyrin repeat, and PH domain. GIT = G protein receptor kinase (GRK) interacting ArfGAP. SMAP = Small ArfGAP.

List of proposed discontinued acronyms: APP = ArfGAP putative, PIX1-interacting, paxillin binding protein. CAT = Cool-associated tyrosine phosphorylated protein. CTGLF = Centaurin gamma-like family. DEF = differentiation-enhancing factor. HRB = HIV Rev binding protein. PAG = paxillin associated Arf GAP. PAP = Pyk2 associated protein. PKL = paxillin-kinase linker. RAB = HIV Rev-associated binding protein. RIP = HIV Rev-interacting protein.

indications when more than one splice variant is known to exist. The 31 predicted human ArfGAPs have been classified into 10 subfamilies, based on sequence similarities of their ArfGAP domains, and supported by the conservation of the domain architecture within each subfamily (see Fig. 1 A). The acquisition of additional domains throughout eukaryotic evolution has contributed to the acquisition of new functions by different ArfGAPs. A brief summary of each subfamily is presented below.

ArfGAP1 subfamily

This founder of the ArfGAP family is also the smallest member, at ∼45 kD. ArfGAP1 shuttles between cytosol and the Golgi, where it is involved in regulating the COPI mechanism of membrane traffic. The region of ArfGAP1 C-terminal to the ArfGAP domain is predicted to be largely unstructured. This region contains two stretches, termed ALPS motifs, that have the propensity in vitro to fold into amphipathic α-helices upon interaction with membranes that are highly curved or contain loosely packed lipids (Bigay et al., 2005; Mesmin et al., 2007), and are required for Golgi targeting of the protein in vivo (Levi et al., 2008). The ALPS motifs are predicted to orient the protein on the membrane and to contribute substantially to regulation of its activity in cells. ArfGAP activity is also regulated by the COPI coat complex (Goldberg, 1999). While most studies have focused on the role of ArfGAP1 in the COPI system, ArfGAP1 also interacts with components of clathrin coated carriers (including clathrin, AP-1, and AP-2), although the functional consequences of these interactions remains to be established.

ArfGAP2 subfamily

ArfGAPs 1–3 are predicted to have arisen from a common ancestor (e.g., a single gene is present in *G. lamblia*) with an early split into distinctive ArfGAP1 and ArfGAP2 subfamilies and later duplications leading to the ArfGAP2/ArfGAP3 divergence. Human ArfGAP2 and 3 are closely related proteins (58% identity) with little similarity to ArfGAP1 outside the catalytic domain. ArfGAP1 and ArfGAP2/3 display functional interplay, as indicated by synthetic lethality observed between these ArfGAPs in HeLa cells (Frigerio et al., 2007), and in *S. cerevisiae* (Gcs1 and Glo3; Poon et al., 1999). ArfGAP2/3 lack ALPS motifs but are found on Golgi membranes as a result of strong interactions with the COPI coat (Watson et al., 2004; Frigerio et al., 2007). Like ArfGAP1, the GAP activities of ArfGAP2/3 are stimulated by coatomer (unpublished data). How each of these ArfGAPs contributes to the COPI mechanism remains unclear.

ADAP subfamily

ADAP1 (ArfGAP with dual PH domains; previously centaurin α1, p42(IP_4), or PIP_3BP) was identified as a high affinity $PI(3,4,5)P_3$ and $Ins(1,3,4,5)P_4$ binding protein. ADAP1 is proposed to function as an Arf6 GAP that regulates the actin cytoskeleton, membrane traffic, and neuronal differentiation (Thacker et al., 2004; Venkateswarlu et al., 2004). ADAP1 localizes to dendrites, spines, and synapses of developing and adult neurons and can impact traffic of regulated secretory vesicles in neuronal cells. Studies of ADAP2 have not been reported.

SMAP subfamily

SMAPs have been implicated as regulators of endocytosis and oncogenesis (Tanabe et al., 2006). Human SMAPs are ∼50 kD and lack other defined domains, thus the acronym small ArfGAP protein. The two human SMAP proteins share 47% identity overall, which rises to 83% identity in the ArfGAP domain. SMAPs bind to clathrin heavy chain via the clathrin binding motif (LLGLD) as well as the clathrin assembly protein, CALM (Natsume et al., 2006). SMAP1 is cytosolic but is recruited to membranes where it regulates constitutive endocytosis. SMAP2 is more stably bound to endosomes and is involved in the retrograde transport of TGN46 from early endosomes to the TGN (Natsume et al., 2006).

AGFG subfamily

AGFG1 has been reported to be an essential HIV Rev cofactor, based on experiments that suggest that the ArfGAP domain mediates the release of Rev-directed HIV-1 RNAs from the perinuclear region (Sanchez-Velar et al., 2004). The Rev–AGFG1 interaction is indirect and possibly bridged by the nuclear export receptor CRM1. The AGFG subfamily arose very early in eukaryotes, with a predicted progenitor in *G. lamblia* and representatives in molds, plants, fish, and mammals. AGFG1 contains 10 phenylalanine-glycine (FG) repeats, reminiscent of those found in nucleoporins. Thus, the AGFGs are ArfGAPs with FG repeats. Much less information is available on AGFG2.

GIT subfamily

GIT genes arose in animals and were duplicated in vertebrates. GIT2 expression is nearly ubiquitous, whereas GIT1 appears absent from many major cell types (muscle, hepatoctyes, pneumocytes, adipocytes) but is especially prominent in endothelial cells (Schmalzigaug et al., 2007). Unlike other ArfGAPs, GITs tightly associate with a specific partner, the PIX/Cool proteins, to form oligomeric complexes (Premont et al., 2004). PIX/Cool proteins are GEFs for Rac1 and Cdc42 GTPases. GIT/PIX complexes function as scaffolds for a variety of signaling enzymes (including G protein receptor kinases, p21 activated kinases, focal adhesion kinases, MEK/Erk, and phospholipase Cγ) and are recruited to distinct cellular locations via specific partners (e.g., focal adhesions via paxillin or integrinα4, synapses via piccolo or liprin-α, and plasma membranes via scribble) (Hoefen and Berk, 2006). GIT/PIX complexes function as sites of signal integration from multiple GTPase inputs, a feature shared by the ARAPs (see below).

ASAP subfamily

The ASAPs are associated with plasma membrane specializations (e.g., focal adhesions and invadopodia), and regulate aspects of endocytic traffic and actin remodeling (Nie and Randazzo, 2006; Inoue and Randazzo, 2007; Randazzo et al., 2007). ASAPs are found exclusively in animals, and have been duplicated in vertebrates, with three genes in humans that share multiple domains (see Fig. 1 A) but differ in their C termini. ASAP1 has tandem repeats of [D/ELPPKP] and an SH3 domain, ASAP2 has an SH3 domain but no E/DLPPKP repeats, and ASAP3 has neither of these motifs. These differences at the C termini have

led to confusion in nomenclature, but phylogenetic analysis of the ArfGAP domains supports the conclusion that these three ASAPs form a distinct group.

ASAP1 was identified as a Src-binding protein but also binds CrkL, focal adhesion kinase, CD2AP, and CIN85 (Inoue and Randazzo, 2007). ASAP2 binds pyk2, a focal adhesion kinase, whereas ASAP3 associates with focal adhesions and regulates stress fibers (Ha et al., 2008).

AGAP subfamily

AGAPs are present in animals only and there are 11 human genes predicted to encode AGAP-type proteins, arising from amplifications in regions of human chromosome 10q, with a number of pseudogenes predicted in this same region. AGAPs possess a GTP-binding domain, reported to directly bind and activate Akt and other Ras effectors (Ye and Snyder, 2004). AGAP2 has multiple splice variants with one possessing an SH3 binding motif N-terminal to the GTP-binding protein-like domain. AGAP1 and AGAP2 have been the most extensively characterized members of this group. They function in the endocytic system; AGAP1 working with AP-3 and AGAP2 with AP-1 (Nie and Randazzo, 2006).

ACAP subfamily

ACAPs regulate Arf6-dependent actin remodeling and endocytosis and receptor tyrosine kinase-dependent cell movement (Inoue and Randazzo, 2007). ACAP1 functions as part of an Arf6-regulated clathrin coat (Li et al., 2007). ACAPs are found in *Dictyostelium* and metazoans, with vertebrate duplications resulting in three human genes. ACAP is an acronym for ArfGAP with coiled coil, ankyrin repeat, and PH domains, though the coiled coil domain was later identified as a BAR domain.

ARAP subfamily

The presence of ArfGAP, RhoGAP, ankyrin repeats, and Ras association domains in ARAPs intimates that they are important coordinators of two or more GTPase signaling pathways. Although the domain structures of the three ARAPs are similar, the proteins are distinct in functions and cellular locations with individual ARAPs showing different Arf, Rho, and Ras binding specificities. Pathways affected by different family members include signaling through EGF receptor, focal adhesion dynamics, and lamellipodia formation (Inoue and Randazzo, 2007; Randazzo et al., 2007). ARAPs are specific to chordates, with three human genes.

Summary

ArfGAPs play critical roles in secretory and endocytic membrane traffic as well as actin remodeling. Other ArfGAPs serve as scaffolds for cell signaling, allowing them to mediate cross-talk between members of different GTPase families. Future studies aimed at dissecting ArfGAP functions and at identifying sources of specificity and regulation in their actions are certain to provide important insights into the role of ArfGAPs in cell physiology and in human pathologies. These outcomes should be facilitated by rapid adoption of the consensus nomenclature described herein.

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