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## Summary

The septins make up a family of guanine-nucleotide binding proteins, most of which polymerize to form filaments. Septin genes have been found in fungi and animals but not in protozoa or plants; yeasts have seven septin genes and humans have twelve, but *Caenorhabditis elegans* has only two. Some septin genes generate multiple polypeptides by alternative splicing or alternative translation start sites. Of the five conserved motifs found in other members of the GTPase superfamily, three are highly conserved in septins. Septin filaments are thought to form a cytoskeletal system that organizes higher-order structures by self-assembly and templated assembly. These multifunctional proteins are best known for their role in cytokinesis, but other functions in dividing and non-dividing cells have evolved in different lineages: budding yeast has septins specific for sporulation; nematode septins are implicated in postembryonic morphogenesis of multiple cell lineages; fly septins are associated with the development of germ cells, photoreceptor cells and nervous system; and mammalian septins are implicated in exocytosis, tumorigenesis, apoptosis, synaptogenesis and neurodegeneration.

The septin genes were originally discovered through genetic screening for budding yeast mutants defective in the cell-cycle progression [1]. Mutants of any one of the genetic loci *CDC*<sub>3</sub>, CDC10, CDC11 or CDC12 commonly form multinucleated cellular clusters [2-4]. These mutants cannot organize the 'bud neck filaments' that normally encircle and demarcate the cell cortex between a mother cell and the bud (daughter) [5]. From these and other data, the septins have been regarded as the major constituents of the bud-neck filaments, which have essential roles in cytokinesis [2-4]. Molecular genetic studies revealed that the four CDC genes encode similar polypeptides, each with some of the set of conserved motifs found in GTPases. The four encoded proteins, termed septins, thus founded a protein family within the GTPase superfamily [2-4]. The septins that were later found in other fungi, nematodes, flies, and mammals have also been shown to have roles in cytokinesis and other cellular processes.

# Gene organization and evolutionary history

Septins have been found in diverse eukaryotes, including animals and fungi but not protozoa and plants. Most septin genes generate one or more polypeptides by alternative splicing and/or multiple translation start sites; the number of variants is not yet established for many of the genes. The septin genes in five organisms, and the largest product of each gene known from the current databases, are shown in Table 1, and a phylogenetic tree illustrating their structural relationships and molecular evolution is shown in Figure 1. It is noteworthy that considerable diversity has been generated within each species; for example, the human septins are 39-63% identical to human Sept2 at the amino-acid level. It may be possible to classify the septins in each species into two to four groups by sequence homology. Orthologs can be found within the fungi (such as Saccharomyces cerevisiae CDC3, Schizosaccharomyces pombe Spn1 and their Candida albicans orthologs, not shown) and within metazoa (such as Drosophila Sep1 and mammalian Sept2), but not between distant lineages (fungi and metazoa). This pattern suggests that there have been independent expansions of the family in different lineages. Thus, any rules and functions found in the fungal septin systems may not necessarily apply to the metazoan ones, and vice versa.

#### Table I

#### The septin genes and proteins in five representative organisms

Species	Approved gene name	Chromosomal location*	Size (amino acids)	Mass (kDa)	lsoelectric point (pl)	Charge	Number of predicted coiled coils	Accession number
Saccharomyces cerevisiae	Cdc3	XII:764137	520	60.0	5.3	А	2	L16548
	Cdc10	III:118342	322	37.0	5.6	А	0	L16549
	Cdc I I	X:576294	415	47.6	4.8	А	I	L16550
	Cdc12	VIII:328038	407	46.7	8.2	В	I	L16551
	Spr3	VII:607564	512	59.8	7.3	Ν	3	U24129
	Spr28	IV:905043	423	48.2	5.8	А	I	NP_010504
	Shs I /Sep 7	IV:52446	551	62.6	5.3	А	2	Z74273
Schizosaccharomyces pombe	spn l	l:1067997	469	53.7	5.3	А	I	U31742
	spn2	l:960487	331	38. I	8.0	В	0	U29888
	spn3	II:2682372	412	46.6	4.7	А	I	U29889
	spn4	l:1962024	380	44.7	7.0	Ν	I	U29890
	spn5	l:3044705	464	53.I	8.2	В	I	U29891
	spn6	III:421493	380	44.0	6.9	Ν	I	AL032824
	spn7	II:161221	428	49.2	5.2	А	0	AF417166
Caenorhabditis elegans	unc-59	1:21.15	459	52.9	8.9	В	L	NM_060987
	unc-6 l	V:6.66	530	60.7	8.9	В	L	NM_182356
Drosophila melanogaster	Pnut	44C2	539	60.2	9.0	В	I	NM_165597
	Sep I	19F5	361	41.1	6.1	А	2	NM_167747
	Sep2	92F2	419	48.5	7.4	Ν	I.	NM_079693
	Sep4	15A1	427	49.0	6.9	Ν	2	NM_167530
	Sep5	43F8	422	48.5	7.3	Ν	I	NM_165578
Homo sapiens	Septl	16p11.1	366	41.8	5.5	А	2	NM_052838
	Sept2	2q37.3	361	41.5	6.2	А	2	NM_004404
	Sept3	22q13.2	345	39.3	6.8	Ν	0	NM_145733
	Sept4	17q23	478	55.I	5.7	А	2	NM_004574
	Sept5	22q11.2	369	42.3	6.4	А	2	NM_002688
	Sept6	Xq24	427	48.9	6.4	А	I.	NM_145799
	Sept7	7q36.1	418	48.8	9.0	В	I.	NM_001788
	Sept8	5q31	483	55.8	5.9	А	I.	XM_034872
	Sept9	17q25.3	586	65.4	9.3	В	0	AF189713
	Sept I 0	8q11.23	517	60.0	6.6	Ν	I.	BC020502
	Sept I I	4q21.22	429	49.4	6.4	А	I.	NM_018243
	Sept I 2	16p13.3	358	40.8	6.7	Ν	0	NM_144605

The data refer to the largest gene products for each gene, deduced from cDNAs on the sequence databases. \*The numbers given for the yeast genes refer to the position of the gene along the sequence of the chromosome. A, acidic (pl < 6.5); B, basic (pl > 7.5); N, neutral. The algorithm COILS [56,57] was used to predict coiled coils, and the peaks above an arbitrary threshold (p > 0.8 at a window size of 14) were counted. The mouse genome has counterparts to each of the 12 human septin genes (not shown). For comparative nomenclature of the mouse and human Sept1-Sept10 genes and the products, see [58].

# **Characteristic structural features**

The full-length septin cDNAs in the current sequence databases encode polypeptides of 30-65 kDa. Most of these gene products have a set of GTPase motifs, G-1, G-3 and G-4, found in members of the GTPase superfamily, (Figure 2 and not shown). The GTPase motifs of the septins are closer to those of the Ras family than of other members of the GTPase superfamily [6] such as the other cytoskeletal GTPases, tubulins in eukaryotes or FtsZ in bacteria. The G-1 motif (which has a consensus in the superfamily of GxxxxGK[S/T] in the single-letter amino-acid code) is well conserved, and the consensus around the G-1 motif of septins is **GESGLGK-S**TLINTLF (where the bold residues are strictly conserved). The G-3 motif (DxxG) is moderately conserved, with the



### Figure I

A phylogenetic tree of the septins in Saccharomyces cerevisiae (Sc), Schizosaccharomyces pombe (Sp), Caenorhabditis elegans (Ce), Drosophila melanogaster (Dm) and humans (Hs). The longest amino-acid sequence among the putative polypeptides generated by each gene was analyzed with the software Phylip [59] using the default mode with the UPGMA method, 1,000 bootstrap replicates and systematic tie-breaking, and Poisson-corrected distances with proportionally distributed gaps. The numbers of predicted coiled coils are shown in parentheses. The scale bar represents 0.1 substitutions.

consensus sequence DTPG; the G-4 motif (xKxD) is strictly conserved with a unique septin consensus of AKAD. The G-2 and G-5 regions cannot be defined in septins; some other classes of GTPases also lack these motifs. GTPbinding and GTP-hydrolyzing activities of the purified and recombinant septin complexes or polypeptides have been demonstrated *in vitro* ([7-11] and M.K., C.M. Field, M.L. Coughlin and T.J. Mitchison, unpublished observations). The biochemical and biological significance of septin GTPase activity remains a conundrum in the field, however.

Septins polymerize to form rod-shaped hetero-oligomeric complexes, which in turn are arranged in tandem arrays to form filaments that appear by electron microscopy to be

	230	240	250	260	270	280	290 <sup>T</sup>	300	310	320	330
CeUnc-61			G <mark>RL</mark>	4Q <mark>lnghv</mark> gfds	LPHQ <mark>LVKK</mark> A	VEAGFQFNLM	C <mark>V</mark> GETGTG <mark>K</mark> TT	LIESLFNMF	LDFEPC		
HsSept6			CRT	<mark>/PLAGHV</mark> GFDS	LPDQLVNKS	VSQG <mark>F</mark> CFNIL	C <mark>VGETGLGK</mark> ST	LMDTLFNTF	(FEGE <mark>PA</mark>		
ScCdc3p			<mark>i kfi</mark> ri	RQ <mark>I</mark> NGY <mark>VGFA</mark> N	ILPKQWHRRS	IKNG <mark>FSFNLL</mark>	C <mark>VGPDGIGK</mark> TT	LMKTLFNNI	D <mark>IEANLVK</mark> D	YEEE <mark>LA</mark> NDQEI	EEEGQGE
<i>√s</i> Sept2			<mark>FI</mark> NI	PETPGY <mark>VGFA</mark> N	ILPNQ <mark>VHRK</mark> S	VKKGFEFTLM	VVGESG <mark>l</mark> gkst	LINS <mark>LFL</mark> TI	LY <mark>PERVI</mark>		<mark>PGA</mark>
<i>Hs</i> Sept7			1	KN <mark>LEGY</mark> VGFAN	ILPNQ <mark>VYRK</mark> S	VKRGFEFTLM	VVGESG <mark>l</mark> gkst	LINSLFLTI	LYS <mark>PEY</mark>		<mark>P</mark> GP
CeUnc-59				-EN <mark>PNYWGFA</mark> N	IFPNQ <mark>VFRRA</mark> Y	VKNG <mark>FDF</mark> TLM	VVGRSG <mark>l</mark> gkst	FINTLFLAE	INN <mark>LNEK</mark>		ES <mark>A</mark>
<i>Is</i> Sept9	QEATEAAPSC <mark>V</mark> GDM	ADTPRDAGLI	KQ <mark>APA</mark> SRNEKAI	<mark>PVDF</mark> GY <mark>V</mark> GIDS	ILEQ <mark>MRRKAI</mark>	MKQG <mark>FEF</mark> NIM	VVGQSG <mark>l</mark> gkst	LINTLFKSF	<mark>(ISR-KS</mark> V		QPT
ScCdc10p				Y <mark>v</mark> gfdt	ITNQ <mark>IEHR</mark> L	LKKG <mark>F</mark> QFNIM	VVGQSG <mark>l</mark> gkst	LINTLFASH	<mark>ILIDS</mark> ATG		DD <mark>I</mark>
ScCdc11p				<mark>MSGIIDA</mark> SS	ALRKRKH	LKRG <mark>ITF</mark> TVM	I V GQSGSG <mark>R</mark> ST	FINTLCGQQ	vvdtstt		
ScCdc12p				<mark>vpppv</mark> gisn	ILPNQRYKIV	NEEGGT <mark>F</mark> TVMI	LCGESG <mark>l</mark> gktt	FINTLFQT <mark>V</mark>	<mark>/LKRA</mark> DGQ		Q <sup>hr</sup>
ScSep7p				T <mark>PPI</mark> N	ILFRRKKE	HKRG <mark>I</mark> TYT <mark>MLI</mark>	LCG <mark>PA</mark> GTG <mark>KT</mark> A	FANNLLET	<mark>(IFP</mark> HKYQYG	KSN <mark>ASI</mark> SSN <mark>P</mark> I	EV <mark>K</mark> VIAP
Consensus	QE <mark>ateaap</mark> sc <mark>v</mark> gdmi	ADT <mark>PRDA</mark> GLI	(Q <mark>APA</mark> S	. GY <mark>V</mark> GF N	ILP Q. RK	.K GF.FT.M	.VG SG <mark>l</mark> gkst	LINTLF .	<b>.</b> .	1	E
	340	350	360	370	380	G-3:DXX0 390	g 400	410	420	430	440
CeUnc-61		1	HELKTVELRTO	CTKDVAEG	G <mark>I</mark>	RVKLRLVETA	GFGDQLDKD-K	SAKVIVDYI	ESQFETYLQ	EELKP-RRML	QYFNDSR
<i>ls</i> Sept6		5	CHTQPGVQLQS1	NTYDLQES	NV	RLKLTIVSTVO	GFGDQINKE-D	SYKPIVEFI	DAQFEAYLQ	EELKI-RRVL	HTYHDSR
<i>c</i> Cdc3p	GHENQS	(	DEORHKVKIKS	ESVIEEN	G <mark>V</mark>	<b>KLNLNVIDTE</b>	G <mark>FGDFL</mark> NNDQK	SWDPIIKEI	DSRFDQYLD	AENKINRHSI	NDKR
<i>ls</i> Sept2	<b>A</b>	1	EKIERTVQIEAS	STVEIEER	G <mark>V</mark> I	KLRLTVVDTP(	GYGDAINCR-D	CFKTIISYI	DEQFERYLH	DESGLNRRHI	IDNR
<i>ls</i> Sept7	S	1	IRIKKTVQVEQS	SKVLIKEG	GV	QLLLTIVDTPO	GFGDAVDNS-N	CWQPVIDYI	DSKFEDYLN	AESRVNRRQM	PDNR
2eUnc-59	PT	1	IPHPSTVRVEE	CLVKLVEN	s <mark>v</mark>	SLNLTLVDTP	GFGDAVNNS-K	CWEPIVNY	ESKFFEQFC	EETRIDRGEK	IVDKC
<i>Is</i> Sept9	SE	1	SRIPKTIEIKS:	THDIEEK	G <mark>V</mark>	RMKLTVIDTP	GFGDHINNE-N	CWQPIMKFI	NDQYEKYLQ	EEVNINRKKR	IPDTR
<i>c</i> Cdc10p	SA	<mark>1</mark>	PVTKTTEMKI	STHTLVED	<mark>RV</mark> I	RLNINVIDTPO	GFGDFIDNS-K	AWEPIVKYJ	KEQHSQYLR	KELTAQRERF	ITDTR
<i>c</i> Cdc11p	ILLPTD	5	ISTEIDLQLREN	TVELEDDE	G <mark>V</mark> I	KIQLNIIDTPO	GFGDSLDNS-P	SFEIISDYI	RHQYDEILL	EESRVRRNPR	FKDGR
3cCdc12p	Q	1	EPIRKTVEIDI	TRALLEEK	HF	ELRVNVIDTPO	GFGDNVNNN- <mark>K</mark>	AWQPLVDFI	DDQHDSYMR	QEQQPYRTKK	FDLR
ScSep7p	TKVVSFNSKNGIPS	VSEFDPMR	ANLEPGITITS:	rs <mark>lel</mark> ggnkdQ	GKPEMNEDD	TVFFNLIMTH(	GIGENLDDS-L	CSEEVMSYI	EQQFDIVLA	EETRIKENPE	FEDTR
Consensus	. NSKNG <mark>IP</mark> S	Y <mark>VSEFDPMR</mark>	TV	.T <mark>L</mark> E. DQ	QG <mark>KP</mark> EMNEG <mark>V</mark>	.L LIDTPO	G <mark>FGD .</mark> NN.Q	.W PI. YI	. Q <mark>F. YL</mark>	EER.	. D.R
	450	460	470 <sup>G-4</sup>	480 480	490	500	510	520	530	540	550
CeUnc-61	IHACLYFISPTGHG	LKALDLVTLI	RELAKRVNVIP	IAKSDTTCKD	DELLRFKAKI	LSELKSQKID	IYTFPTDD	-ETV	STTNK	EMNKSVPFAV	VGSIDFV
<i>ls</i> Sept6	IHVCLYFIAPTGHS	LKSLDLVTM	<b>KKLDSKVNIIP</b>	IIAKADAISKS	ELTKFKIKI	ISELVSNGVQ:	IYQFPTDD	-ES <mark>V</mark>	<mark>AEI</mark> NG	TMNAHLPFAV	IGSTEEL
ScCdc3p	IHACLYFIEPTGHYI	LKPLDLKFM	2SVYEKCNLIP	/IAKSDILTDE	EILSFKKTI	MNQLIQSNIEI	LFKPPIYSNDD	AEN	SHLSE	RLFSSLPYAV	IGSNDIV
<i>ls</i> Sept2	VHCCFYFISPFGHG	LKPLDVAFM	KAIHNKVNIVPY	/IAKADTLTLK	ERER <mark>LKKR</mark> II	LDEIEEHNIK:	IY <mark>HLPDA</mark> ESDE	DEDF	<mark>KEQTR</mark>	LLKAS IPF SV	VGSNQ <mark>LI</mark>
<i>Hs</i> Sept7	VQCCLYFIAPSGHG	LKPLDIEFM	KRLHEKVNI I PI	LIAKADTLTPE	ECQQ <mark>FKKQ</mark> II	MKEIQEHKIK:	IYEFPETD-DE	EE	NKLVK	KIKDRLPLAV	VGSNTII
CeUnc-59	VHLCLYFIEPSGHG	LKPIDIELM	KHLHGRVNIVPY	<mark>/ISKADCLTR</mark> D	ELLRFKKQI	VKDAET <mark>AEIK</mark> I	LY <mark>KFPELEDP</mark> Y	TD	<mark>Kvai</mark> e	K <mark>lrk</mark> alpfai	IGSN <mark>ML</mark> K
<i>Is</i> Sept9	VHCCLYFIPATGHS										
			<b>KRLSKVVNIVP</b>	/IAKADTLTLE	ER <mark>VHF</mark> KQR <mark>I</mark>	TADLLSNGID	VY <mark>PQKEF</mark> D-ED	SED	<mark>RLV</mark> NE	<mark>kfre</mark> mipfav	VGSDHEY
ScCdc10p	VHAILYFLQPNGKEI	LSRLDVEAL	KRLSKVVNIVP Krlteianvipy	/IAKADTLTLE /I <mark>gksdtltl</mark> d	ER <mark>VHF</mark> KQRI ERTEFRELI	T <mark>ADLL</mark> SNGID QNEFEKYNFK	VYPQ <mark>KEF</mark> D-ED IYPYDSEE-LT	SED	<mark>RLV</mark> NE <mark>LEL</mark> NR	KFREMIPFAV S <mark>VRS</mark> IIPFAV	VGSDHEY VGSENEI
ScCdc10p ScCdc11p	VHAILYFLQPNGKEI VHCCLYLINPTGHGI	LSRLDVEALI LKEIDVEFII	KRLSKVVNIVP KRLTEIANVIP RQLGSLVNIIP	/IAKADTLTLE /IGKSDTLTLD /ISKSDS <mark>L</mark> TRD	ERVHFKQRI DERTEFRELI DELKLNKKLI	TADLLSNGIDY DNEFEKYNFK MEDIDRWNLP:	VYPQKEFD-ED IYPYDSEE-LT IYNFPFDEDEI	SED DEE SDED	<mark>RLV</mark> NE <mark>LEL</mark> NR YETN <mark>M</mark>	KFREMIPFAV SVRSIIPFAV Y <mark>LRTLLPFAI</mark>	VGSDHEY VGSENEI IGSNEVY
S <i>c</i> Cdc10p S <i>c</i> Cdc11p S <i>c</i> Cdc12p	VHAILYFLQPNGKEI VHCCLYLINPTGHGI VHAVLYFIRPTGHGI	LSRLDVEAL LKEIDVEFI LKPIDIETMI	KRLSKVVNIVP KRLTEIANVIP RQLGSLVNIIP KRLSTRANLIP	/IAKADTLTLE /IGKSDTLTLD /ISKSDSLTRD /IAKADT <mark>LTA</mark> Q	ERVHFKQRI DERTEFRELI DELKLNKKLI DELQQFKSRI	T <mark>ADLL</mark> SNGID QNEFEKYNFK MEDIDR <mark>W</mark> NLP RQVIEAQEIR:	VYPQKEFD-ED IYPYDSEE-LT IYNFPFDEDEI IFTPPLDADSK	SED DEE SDED EDAKSGSN <mark>F</mark>	RLVNE <mark>LEL</mark> NR YETNM PDS <mark>AAVEHA</mark> R	KFREMIPFAV SVRSIIPFAV YLRTLLPFAI QLIEAMPFAI	VGSDHEY VGSENEI IGSNEVY VGSEKK <mark>F</mark>
GcCdc10p GcCdc11p GcCdc12p GcCep7p	VHAILYFLQPNGKEJ VHCCLYLINPTGHGI VHAVLYFIRPTGHGJ VHVALYFIEPTGHGJ	LSRLDVEALI LSRLDVEALI LKEIDVEFII LKPIDIETMI LREVDVELMI	KRLSKVVNIVPY KRLTEIANVIPY ROLGSLVNIIPY KRLSTRANLIPY KSISKYTNVLP:	/IAKADTLTLE /IGKSDTLTLD /ISKSDSLTRD /IAKADTLTAQ IITRADSFTKE	ERVHFKQRI DERTEFRELI DELKLNKKLI DELQQFKSRI ELTQFRKNI	T <mark>adllsngidy</mark> Qnefekynfk Medidrwnlf RQVIEAQEIR Mfdverynvp	VYPQKEFD-ED IYPYDSEE-LT IYNFPFDEDEI IFTPPLDADSK IYKFEVDPEDD	SED DEE SDED EDAKSGSN <mark>F</mark> DLES	RLVNE LELNR YETNM PDS <mark>AAVEHAR</mark> MEENQ	KFREMIPFAV SVRSIIPFAV YLRTLLPFAI QLIEAMPFAI ALASLQPFAI	VGSDHEY VGSENEI IGSNEVY VGSEKKF ITSDTRD
GcCdc10p GcCdc11p GcCdc12p GcSep7p Consensus	VHAILYFLQPNGKEJ VHCCLYLINPTGHGJ VHAVLYFIRPTGHGJ VHVALYFIEPTGHGJ VH.CLYFI PTGHGJ	LSRLDVEALI LKEIDVEFII LKPIDIETMI LREVDVELMI LKPLD.E.MI	KRLSKVVNIVP KRLTEIANVIPP ROLGSLVNIIP KRLSTRANLIP KSISKYTNVLP K.L. VNIIP	/IAKADTLTLE /IGKSDTLTLD /ISKSDSLTRD /IAKADTLTAQ IITRADSFTKE /IAKADTLT .	ERVHFKQRI DERTEFRELI DELKLNKKLI ELQQFKSRI ELTQFRKNI EL FKK I	TADLLSNGIDV QNEFEKINFKI MEDIDRWNLP RQVIEAQEIR MFDVERINVP	VYPQKEFD-ED IYPYDSEE-LT IYNFPFDEDEI IFTPPLDADSK IYKFEVDPEDD IY FP	SED DEE SDED EDAKSGSNF DLES E SGSNF	RLVNE LELNR YETNM PDSAAVEHAR MEENQ PDSAAE.N	KFREMIPFAV SVRSIIPFAV YLRTLLPFAI QLIEAMPFAI ALASLQPFAI LPFAV	VGSDHEY VGSENEI IGSNEVY VGSEKKF ITSDTRD VGS
ScCdc10p ScCdc11p ScCdc12p ScSep7p Consensus	VHAILYFLQPNGKEJ VHCCLYLINPTGHGJ VHAVLYFIRPTGHGJ VHVALYFIEPTGHGJ VH.CLYFI PTGHGJ 560	LSRLDVEALI LSRLDVEALI LKEIDVEFII LKPIDIETMI LREVDVELMI LKPLD.E.MI	RLSKVVNIUP (RLTEIANVIP) (RLSTRANLIP) (SISKYTNVLP) (.LVNIIP) 580	/IAKADTLTLE /IGKSDTLTLD /ISKSDSLTRD /IAKADTLTAQ IITRADSFTKE /IAKADTLT . 590	ERVHFKQRI DERTEFRELI DELKLNKKLI DELQQFKSRI ELTQFRKNI EL FKK I 600	TADLLSNGIDV DNEFEKYNFK: MEDIDRWNLP RQVIEAQEIR: MFDVERYNVP I : 610	VYPQKEFD-ED IYPYDSEE-LT IYNFFFDEDEI IFTPPLDADSK IYKFEVDPEDD IYFP	SED DEE SDED EDAKSGSNE DLES E SGSNE 630	RLVNE LELNR YETNM PDSAAVEHAR MEENQ PDSAA E.N 640	KFREMIPFAV SVRSIIPFAV YLRTLLPFAI QLIEAMPFAI ALASLQPFAI LPFAV 650	VGSDHEY VGSENEI IGSNEVY VGSEKKF ITSDTRD VGS 660
GoCdc10p GoCdc11p GoCdc12p GoCsep7p Consensus CoUnc-61	VHAILYFLQPNGKEJ VHCCLYLINPTGHGJ VHAVLYFIRPTGHGJ VHVALYFIEPTGHGJ VH.CLYFI PTGHGJ 560 KKENG-QMVRARQY	LSRLDVEALI LKEIDVEFII LKPIDIETMI LREVDVELMI LKPLD.E.MI 570 PWGIVEVEN	RLSKVVNIP RLTEIANVIP QLGSLVNIP (RLSTRANLIP) (SISKYTNVLP) (SLVNIIP) 580 ESHCDFVKLRE	VIAKADTLTLE VIGKSDTLTLD VISKSDSLTRD VIAKADTLTAQ IITRADSFTKE VIAKADTLT . 590 ALLRTNVDEM	ERVHFKORI DERTEFRELI DELKLNKKLI DELQQFKSRI ELTQFRKNI EL FKK I 600 RQRTHESLYE	TADLLSNGID QNEFEKYNFK MEDIDRWNLP RQVIEAQEIR MFDVERYNVP I 610 NYRRDRLRQM	VYPQKEFD-ED IYPYDSEE-LT IYNFPFDEDEI IFTPPLDADSK IYKFEVDPEDD IY FP 620 KIG-DGETGPI	SED DEE SDED EDAKSGSNE DLES ESGSNE 630	RLVNE LELNR YETNM PDSAAVEHAR MEENQ -DSAA E.N 640	KFREMIPFAV SVRSIIPFAV YLRTLLPFAI QLIEAMPFAI ALASLQPFAI LPFAV 650	VGSDHEY VGSENEI IGSNEVY VGSEKKF ITSDTRD VGS 660 IIEKLAQ
GoCdc10p GoCdc11p GoCdc12p GoCsep7p Consensus CoUnc-61 HsSept6	VHAILYFLQPNGKEI VHCCLYLINPTGHG VHAVLYFIRPTGHG VHALYFIEPTGHG VH.CLYFI PTGHG 560 KKENG-QMVRARQY KIGNKMRRARQY	LSRLDVEALI LKEIDVEALI LKEIDVEFIN LKPIDIETMI LREVDVELMI LKPLD.E.MI 570 PWGIVEVEN PWGIVEVEN	CRLSKVVNIVP CRLTEIANVIP QLGSLVNIPY KSISKYTNVLP K.L. VNIIP 580 ESHCDFVKLRE EAHCDFVKLRE	VIAKADTLTLE VIGKSDTLTLD VISKSDSLTRD VIAKADTLTAQ LITRADSFTKE VIAKADTLT 590 ALLRTNVDEMI MLIRVNMEDL	ERVHFKQRI DERTEFRELI DELKLNKKLI DELQQFKSRI ELTQFRKNI EL FKK I 600 RQRTHESLYE REQTHTRHYE	TADLLSNGID QNEFEKYNFK MEDIDRWNLP RQVIEAQEIR MFDVERYNVP I 610 NYRRDRLRQM LYRRCKLEEM	YYPQKEFD-ED IYPYDSEE-LT IYNFPFDEDEI IFTPPLDADSK IYKFEVDPEDD IY FP 620 IKIG-DGETGPI IGFK-DTPPDSI	SED DEE SDED EDAKSGSNE DLES E SGSNE 630 X KPF	RLVNE YETNM PDSAAVEHAR MEENQ PDSAA E.N 640	KFREMIPFAV SVRSIIPFAV YLRTLLPFAI QLIEAMPFAI ALASLQPFAI LPFAV 650	VGSDHEY VGSENEI IGSNEVY VGSEKKF ITSDTRD VGS 660 IIEKLAQ IQETYEA
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Soc dc 10p Soc dc 11p Soc dc 12p Soc Sep7p Consensus Colunc-61 AsSep16 Soc dc 3p AsSep12	VHAILYFLQPNGKEI VHCCLVLINPTGHG VHCLVFIRPTGHG VHVALYFIRPTGHG VH.CLYFI PTGHG 560 KKENG-QMVRARQY KIGNKMKRARQY ENYSG-NQVRGRSY EAKGKKVRGRLY	LSRLDIEFMI LSRLDVEALI LKEIDVEFII LKEUDVELMI LKPLD.E.MI 570 PWGIVEVEN PWGVVEVEN PWGVVEVEN	KRLSKVUNIVPI (RLTEIANUIP) (RLSTRANLIP) (SISKYINVLP) (L. VNIP) 580 ESHCDFVKLRE EAHCDFVKLRE DNHSDFNLLKN PEHNDFLKLRT	VIAKADTLTLE VIGKSDTLTLD VISKSDSLTRD VIAKADTLTAQ LITRADSFTKE VIAKADTLT . 590 ALLRTNVDEMI MLIRVNMEDLI LLIKQFMEELI MLI-THMQDLQ	ERVHFKQRI DERTEFREI DELKLNKKLI DELQQFKSRI ELTQFKKNI ELFKKI 600 RQRTHESLYE REQTHTRHYE KERTSKILYE QEVTQDLHYE	TADLLSNGID ONEFEKYNFK MEDIDRWNLP ROVIEAOEIR MFDVERYNVP I 610 NYRRDRLROM LYRRCKLEEM NYRSSKLAKL	VYPQKEFD-ED IYPYDSEE-LT IYPFPPDEI IFTPPLDADSK IYKFEVPEDD IYFP 620 IKIG-DGETGPI GIK-QDETGPI GIK-QDNSVFI GRK-VENEDMI	SED DEE EDAKSGSNE DLES E SGSNE 630 K KEFDP NKD	RLVNE 	KFREMIPFAV SVRSIIFFAV YLRTLLPFAI QLIEAMFFAT ALASLQPFAI LPFAV 650 	VGSDHEY VGSENEI IGSNEVY VGSEKKF ITSDTRD VGS 660 IIEKLAQ SLQETYEA KQQE
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Code 10p Code 11p Code 11p Code 12p Consensus Colume-61 AsSep16 Code 3p AsSep12 AsSep17 Colume-59 AsSep19 Socder12p Socder12p Socder12p Consensus Codume-61 AsSep16 Socder3p	VHAILYFLQPNGKEJ VHCCLYLINPTGHG VHAVLYFIRPTGHG VHVALYFIRPTGHG S60 KKENG-QMWRARQY KIGN-KMWRARQY ENYSG-NQVRGSY EXKG-KKVRGLY EXKG-KKVRGLY EXKG-KKVRGLY QVNG-KRILGRKT EING-ETFRGRKT ENGGOVGTIRGRKY SEGRYVR-EY E.GGV VRGR Y 670 KHREHQDEFSRREL KRNEFLGELQKKEE EKTLHEAKLAKLEI	LSRLDVEALI LSRLDVEALI LKEIDVEALI LREVDVELMI LREVDVELMI S70 PWGIVEVEN PWGTVQVEN PWGVEVEVEN PWGVEVEVEN RWSAINVED PWGILDVED PWGILDVED PWGILDVED PWGISIDD PWGEVEN 680 TLRE EMRQ	KRLSKVUNIVPI (RLSTRANLIPV (RLSTRANLIPV (SISKYTNULP) (S	VIAKADTLTLE VIGKSDTLTLD VISKSDSLTRD VIAKADTLTAQ UITRADSFTKE VIAKADTLT . 590 ALLRTNVDEMI MLIRVNMEDLI LLKQFMEELI MLIRTHMQDLQ MLIRTHMQDLQ MLIRTHMQDLQ LLRTHLQDL ALLISHLHDL] LLRTHLQDL ALLISHLHDL] VUFGSHLQEFI .LIRTH DL 700 DMRKVEECLAI	ERVHFKQRI SERVHFKQRI SELKLNKKLI SELVQFKSRI ELTQFRKNI EL FKK I 600 RQTHESLYE REQTHTRHYE KERTSKILYE QEVTQDLEYE KDTNNVHYE KDTTSSIHYE ISTTQEMHYE ISTTQEMHYE ISTTQEMHYE 1STTQEMHYE 710 AREREVH EKFDRLK ARHKEMK	TADLLSNGID QNEFEKYNFK: WEDIDRWNLP: WEDIDRWNLP: GOO NYRRDRLROM LYRRCKLEEM NYRSSKLAKL NYRSSKLAKL NYRSFRQMEGL AYRVKRLNEG GFRARQLIAL RYRVKRLNEG GFRARQLIAL NYRSEKLSSV NYR .L . 720	VYPQKEFD - ED IYPYDSEE - II IYPFDSEE - II IYFFYDEDBI IYFFYDEDBI IYFFYDFDDSK IKIG-DGETGPI GFK - DTPPDS GIK-QDNSVFI GRK - VENEDMI TYN - GVDNKI SS - AMANGVI KEN - ANSRSS SVAAES I RPNI ENTGEGRUEDF ANAEE I GPNS' - 730	SED DEE EDAKSGSNF DES ESGSNF 630 C CFP CEFDP KKD KKD CEFDP CFDP	LSNFASLIST	KFREMIPPAV SVRSIIFAV JLRTLPPAI QLIEAMFFAT ALASLQPFAI 650 	VGSDHEY VGSEKNEI IGSNEVY VGSEKKF ITSDTRD VGS 660 IIEKLAQ VGS FLAQMEE SPLAQMEE SPLAQMEE GSSSSST 
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Figure 2 (see the legend on the next page)

7-9 nm thick. These filaments can assemble in vitro into even higher-order structures by self-assembly and templated assembly. Repeating unit complexes made up of Cdc3p, Cdc10p, Cdc11p, and Cdc12p in budding yeast, Sep1, Sep2 and Pnut in flies, and Sept2, Sept6, and Sept7 in mouse and human have been purified and characterized [4,7,10,12-14]. The majority of septins are predicted to have one or more coiled-coil regions, each spanning about 50-100 amino-acid residues, mostly near the carboxyl termini. In the metazoan septins, proteins that are close on the phylogenetic tree have the same number of coiled coils (Figure 1). Some of the coiled-coil regions are necessary for intermolecular interaction upon septin complex formation [10], whereas others are dispensable ([11,15] and M.K., C.M. Field, M.L. Coughlin and T.J. Mitchison, unpublished observations). Some septins have no predictable coiled-coil region (for example, S. cerevisiae Cdc10p, S. pombe Spn2p and Spn7p, and human Sept3, Sept 9 and Sept12). The mechanism of inter-septin interaction other than through coiled coils is unknown.

The isoelectric points of most septin polypeptides are within the acidic to neutral range, but each organism has one or two septins of basic charge (for example, *S. cerevisiae* Cdc12p, *S. pombe* Spn2p and Spn5p, both *C. elegans* septins, *Drosophila* Pnut and human Sept7 and Sept9; these are indicated in Table 1). The nematode is exceptional in that it has only two septin genes, both of which encode highly basic proteins. The significance of the isoelectric points of septins is currently unknown. Regardless of the total charge, a short stretch of basic residues preceding the G-1 region is shared by most, but not all, of the septins. Some of these basic residues are critical for interactions with phospholipids *in vitro* [9,11].

The budding yeast septins Cdc3p, Cdc11p and Shs1p have one or more motifs for sumoylation, [I/V/L]KX[E/D]; the lysine is the attachment site for the ubiquitin-like protein SUMO. Mutating these sites results in loss of bud-neckassociated SUMO and persistent septin rings [16]. Thus, SUMO conjugation is a prerequisite for septin-ring disassembly. This discovery provided a breakthrough towards an understanding of the regulatory mechanism of yeast septin dynamics, and it also suggests that the significance of the sumoylation motifs found in septins from other organisms should be tested.

# Localization and function

Expression of the septin genes seems to be regulated according to the cell cycle, cell lineage, and developmental

stage. In accordance with a generally accepted notion that the hetero-oligomeric complex is the main functional unit of the septin system [4], the cell-type distributions of different septin proteins largely overlap one another. Paradoxically, however, their subcellular localization is not necessarily identical; this is demonstrated, for example in postmitotic cells in the mouse brain [17]. The differential localization of septin proteins or complexes may reflect their distinct roles *in vivo*. Besides the best-known functions in cytokinesis, the septin system seems to have evolved to fulfill multiple roles in dividing and non-dividing cells. The normal localization, mutant phenotypes, and possible functions inferred from genetic and cell biological data are summarized for key organisms below.

## S. cerevisiae and S. pombe

The 'classical' septins of budding yeast (Cdc3p, Cdc10p, Cdc11p, Cdc12p, and Shs1p/Sep7p) predominantly occur as ring(s) encircling the mother-bud neck, but they also localize at the cell cortices near the presumptive bud site, at the bud scar after cytokinesis, and at the tapering part and the tip of the shmoo, a pheromone-induced protrusion [2,18,19]. As described above, the main phenotype of the original temperature-sensitive mutants (*cdc3, cdc10, cdc11* and *cdc12*) is a lack of bud-neck filaments and cytokinesis defects. The *CDC3* $\Delta$  and *CDC12* $\Delta$  mutants are lethal; the *CDC10* $\Delta$  and *CDC11* $\Delta$  mutants are viable but are unable to organize the bud-neck filaments (the septin ring), and the other septins localize to the bud neck to partially fulfill the functions of the missing septins [12,19].

The septin ring is a multifunctional structure that serves several functions: firstly, as a spatial landmark to establish cell polarity for bud-site selection, in cooperation with other proteins (such as the bud-site selection proteins Bud3p and Bud4p) [20,21]; secondly, as a barrier that prevents bud-specific cortical molecules (Spa2p, Sec3p, Sec5p, Ist2p and others) from diffusing laterally into the mother-cell cortex [22,23]; thirdly, as a scaffold to recruit molecules for cell-wall synthesis (for example, the chitin synthases Chs4p and Chs3p and the scaffold protein Bni4p) [24] and for positioning of the mitotic spindle [25]; and finally, as an apparatus to monitor and control progression of mitosis in conjunction with the cell-cycle regulatory kinases Gin4p, Hs1p and Kcc4p [26-28], and a component of the mitosis exit network, Tem1p [29,30].

The 'non-classical' *S. cerevisiae* septins (Spr3p and Spr28p) are expressed in a temporally limited manner during spore formation and are targeted beneath the developing prospore

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Figure 2 (see the figure on the previous page)

Multiple alignment of the central regions of representative septins. Amino-acid sequences of the representative septins were aligned using MacVector. Acidic, basic and hydrophobic residues are in purple, blue, and yellow respectively. The GTPase motifs that are conserved in this family - G-I, G-3 and G-4 - are indicated above the sequence. A few other conserved stretches of hydrophobic and charged residues are also recognizable. Species abbreviations are as in Figure I.

wall [15,31,32]. Deletion of the *SPR3* or *SPR28* genes causes no obvious phenotype, and a double mutant has minimal defects in sporulation, suggesting that there is compensation by the other septins [15,32].

S. pombe Spn1p, Spn3p, and Spn4p localize to medial ring(s) around the circumference of the dividing cell, where they functionally interact with Mid2p (which is related to the actin-binding protein anillin in animals). The  $spn1\Delta$  and  $spn4\Delta$  mutants show mild cytokinetic defects such as delayed cell-cell separation and accumulation of cells with one or more septa [2,33,34].

## Animals

The *C. elegans* UNC-59 and UNC-61 septin proteins localize to the leading edge of the cleavage furrow and the spindle midbody. Mutants of either or both of them exhibit minimal defects in embryonic cytokinesis, but abnormalities in postembryonic morphogenesis occur in multiple organs; these include vulva protrusion, germ-cell defects including gonad extrusion, egg-laying defects, and deformities in the male tail and male sensory neurons. The uncoordinated movement defect through which the mutants were originally isolated also indicates some functional defects in the mutants' nervous systems. Some of these phenotypes are recapitulated by silencing *unc-59* and/or *unc-61* through siRNA microinjection of small interfering RNAs (siRNAs) [35,36].

In the Drosophila embryo, the Pnut, Sep1, and Sep2 septin proteins have been found in the front of cellularization moving along the early embryo, in the cleavage furrows of dividing cells, and at the leading edges of the epithelium during embryonic dorsal closure. Later in development, they are found in the apical and basal cell cortices of larval imaginal discs, in the cell cortices of the embryonic and larval central nervous system and of photoreceptor cells in the eye imaginal discs [37-39], and in ring canals (stable intercellular bridges formed by incomplete cytokinesis of male and female germ cells) [7,40,41]. The pnut gene was identified as an enhancer of the seven in absentia defect, which results in loss of the R7 photoreceptor cells; pnut-null mutant larvae have severely reduced cell number, with multinucleated cells in the imaginal discs and brain, and they die shortly after pupation [37]. Mutant embryos lacking the Pnut contribution from both the mother and the zygote have abnormal organization of actin rings in the late cellularization stage of embryogenesis and extensive morphological defects during gastrulation and in the formation of cuticle, head, tail, and denticles [39].

Mammalian septins have been found in the cell cortex, contractile ring and midbody of mitotic cells (Sept2, Sept4, Sept6, Sept7, and Sept9) and in the cell cortex, actin stress fibers (Sept2, Sept4, Sept6, Sept7, and Sept9) and micro-tubules (Sept9) of interphase cells ([8,9,13,14,42-46] and M.K., C.M. Field, M.L. Coughlin and T.J. Mitchison,

unpublished observations). In the nervous system, they are seen on the cytoplasmic side of presynaptic membranes (Sept7) and synaptic vesicles (Sept5 and Sept6) and in the endfeet of astroglia (Sept4 and Sept7) [17]. Cytokinesis is perturbed by microinjection of anti-septin antibodies (against Sept2 and Sept9) or transfection of siRNAs (against *Sept2, Sept7, Sept9*) [8,45,46]. Depletion of Sept2 or Sept7 protein by RNA interference also causes disorganization of actin stress fibers, leading to a flat cell morphology in interphase cells [14]. Although Sept5 is highly expressed in mature nervous systems, no brain abnormality is seen in the *Sept5*-null mice, probably because of compensation by redundant septin species [47]. *Sept5*-null mice do, however, aggregate and release granules from blood platelets more readily than do wild-type mice [48].

# **Frontiers**

A number of open questions remain with regard to the septins. Firstly, the fine structures of septins beyond the ultrastructural level are totally unknown. Resolving the atomic structures of septin monomers, oligomers and polymers should help us to address the major questions in septin biochemistry, such as the mechanisms of septin polymer assembly and disassembly and how GTP hydrolysis might be coupled to changes in the structure and activity of the proteins. It will be important to elucidate the mechanisms by which sumoylation and phosphorylation might control septin assembly and disassembly at the structural, biochemical, and cellular levels [16,49].

The interactions of septins with non-septin molecules - such as actin and anillin [8,14,33,34], microtubules [25,45,46], mitosis-associated proteins (see above), and lipids [9,11] should help to reveal their unknown cellular functions and to clarify the mechanisms underlying the events in which they are involved. Likewise, the discovery of new subcellular localizations of septins may also lead to discoveries of novel roles for the proteins, as is illustrated by a mitochondrial septin variant that has been implicated in apoptosis [50].

Many research groups have found independently that two human septin genes from different groups (*Sept6* and *Sept9*; see Figure 1) have translocated to, and fused in-frame with, the mixed lineage leukemia (*MLL*) gene, and that a few human and mouse septin genes (*Sept2*, *Sept4*, and *Sept9*) are amplified and/or aberrantly expressed in a variety of malignancies, including leukemia, lymphoma and solid tumors (see, for example, [51,52]). Although the hypothetical oncogenic activities of these septins and the fusion proteins remain to be tested, exploring the involvement of septins in carcinogenesis should bring novel perspectives to cancer research as well as to septin biology.

As mentioned above, a subset of septins are abundantly expressed in metazoan nervous systems, but the biological

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significance of septins in postmitotic neurons and glial cells has not been understood. Considering the functional redundancy and complexity of the septins, determining their precise roles in neural development and in synaptic or glial functions is challenging, even using systematic genetic analysis including multiple and conditional gene disruption. The septins of nematodes have the potential to lead the field of septin neurobiology, given their relative simplicity.

Finally, in addition to the elusive functions of septins in normal brains, aberrant deposits of septins have been found in neurofibrillary tangles in Alzheimer's disease, in Lewy bodies in Parkinson's disease, and in related pathological aggregates in human brains [53,54]. Exploring the possible linkages between septins and the major players in each disease (such as amyloid-precursor protein, presenilins, and tau proteins in Alzheimer's disease and parkin, the Pael receptor, and synucleins in Parkinson's disease [54,55]) is expected to reveal functions for septins in the brain and help to clarify the unknown pathophysiology underlying these disorders.

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