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Review

Conquering the complex world of human septins: implications for health and disease

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Septins are highly conserved filamentous proteins first characterized in budding yeast and subsequently identified in must eukaryotes. Septins can bind and hydrolyze GTP, which is intrinsically related to their formation of septin hexamers and functional protein interactions. The human septin family is composed of 14 loci, *SEPT1-SEPT14*, which encode dozens of different septin proteins. Their central GTPase and polybasic domain regions are highly conserved but they diverge in their N-terminus and/or C-terminus. The mechanism by which the different isoforms are generated is not yet well understood, but one can hypothesize that the use of different promoters and/or alternative splicing could give rise to these variants. Septins perform diverse cellular functions according to tissue expression and their interacting partners. Functions identified to date include cell division, chromosome segregation, protein scaffolding, cellular polarity, motility, membrane dynamics, vesicle trafficking, exocytosis, apoptosis, and DNA damage response. Their expression is tightly regulated to maintain proper filament assembly and normal cellular functions. Alterations of these proteins, by mutation or expression changes, have been associated with a variety of cancers and neurological diseases. The association of septins with cancer results from alterations of expression in solid tumors or translocations in leukemias [mixed lineage leukemia (MLL)]. Expression changes in septins have also been associated with neurological conditions such as Alzheimer's and Parkinson's disease, as well as retinopathies, hepatitis C, spermatogenesis and Listeria infection. Pathogenic mutations of *SEPT9* were identified in the autosomal dominant neurological disorder hereditary neuralgic amyotrophy (HNA).
Human septin research over the past decade has established their importance in cell biology and human disease. Further functional characterization of septins is crucial to our understanding of their possible diagnostic, prognostic, and therapeutic applications.

EA Peterson[a,b] and EM Petty[a,b]

[a]Department of Human Genetics, and
[b]Department of Internal Medicine,
University of Michigan Medical School,
Ann Arbor, MI, USA

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Corresponding author: Elizabeth M. Petty, MD, Departments of Human Genetics and Internal Medicine, University of Michigan Medical School, 5220 MSRB III, Box 640, 1150 West Medical Center Drive, Ann Arbor, MI 48109-640, USA.
Tel: 734 763 2532;
fax: 734 647 7979;
e-mail: epetty@umich.edu

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Forty years ago, septin's pioneer researchers may have never imagined that their discovery of four novel yeast genes would open the door to a biologically complex world of cytoskeletal GTPases that were highly relevant to human disease. Septins were first characterized in *Saccharomyces cerevisiae* as a group of cytoskeletal GTP-binding proteins essential for proper cell division. Genetic screening performed by Hartwell and colleagues for budding yeast mutants led to the discovery of the first septin genes, *CDC3, CDC10, CDC11* and *CDC12*, in which temperature-sensitive mutations caused defects in budding morphology and cell cycle arrest (1). These genes were further characterized in *Saccharomyces pombe* in which mutations led to cytokinesis defects during mitosis. Subsequently, septins have been found to be highly conserved in all eukaryotes except plants, and many of the loci encode for different variants and/or protein isoforms (Table 1).

Table 1. Human septins variants and isoforms per loci[a]

Human septin loci	Number of recognized variants/isoforms	Variable region(s)
SEPT1	–	–
SEPT2	Four transcripts/one isoform	5′-UTR and 3′-UTR
SEPT3	Two isoforms	3′-UTR and C-termini
SEPT4	Three isoforms	5′-UTR and 3′-UTR, N- and C- termini
SEPT5	–	–
SEPT6	Four isoforms	3′-UTR, C-termini
SEPT7	Two isoforms	Alternative splicing exon 2
SEPT8	Four isoforms	5′-UTR and 3′-UTR, N- and C- termini
SEPT9	Seven transcripts/six isoforms	5′-UTR and 3′-UTR, alternative splicing of 5′ exons
SEPT10	Two isoforms	Alternative splicing exon 2
SEPT11	–	–
SEPT12	Two isoforms	Alternative splicing central exon
SEPT13	–	–
SEPT14	–	–

UTR, untranslated region.
[a]Data gathered from NCBI Reference Sequence (Refseq).

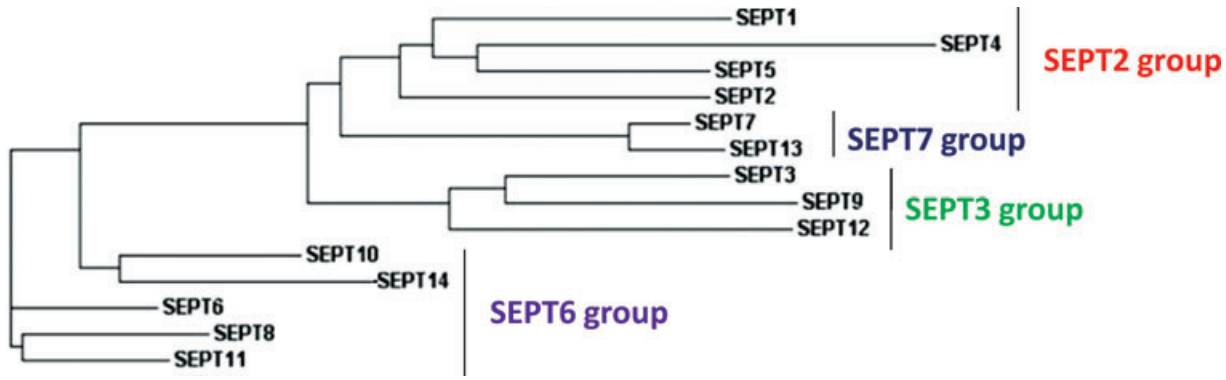

Fig. 1. Phylogenetic tree of the human septin family. A dendrogram tree illustrates the phylogenetic relationship of the human septin family members as determined by Clustal W analysis [modified from Peterson EA, et al. (2007) *Mamm Genome*].

Recently, phylogenetic and evolutionary analysis for septins of metazoans showed that all septin proteins could be clustered into four major subgroups (Fig. 1). It has been proposed that the emergence of these four subgroups occurred before the divergence of vertebrates and invertebrates and that septin expansion in number was due to duplication of pre-existing genes (2). Septin research has grown impressively, from four genes identified in budding yeast to 14 core loci identified in humans to date. The variety of existing septin isoforms and the diversity of their biological functions in eukaryotic cells are both intriguing and exciting. Contributions to septin biology over the last few years include the first crystal structure of septin oligomers, septin protein interactions, expression profiles, associations with well-known signaling pathways and involvement in human disease. These observations have set the stage for more exciting experimental strategies to further understand the role of septins in health and disease. Many questions regarding septins' multiple physiological functions in cells as related to normal development, health, and human diseases still remain.

Human septin family conserved domains

The four human septin subgroups are characterized by sequence homology and domain composition (Figs 1 and 2). All human septins share a highly conserved central region that contains a polybasic domain and the GTP-binding domain. The N- and C-terminal regions vary in length and amino acid composition. They contain a proline-rich domain and an α-helical coiled-coil domain, respectively. The relevance of the differences in the N- and C-termini of some septins and their isoforms is not completely understood, but these variations might play a role in their unique cellular localizations, protein interactions, and biological functions. While the specific functions of these domains remain to be fully elucidated, recent studies have begun to reveal information about

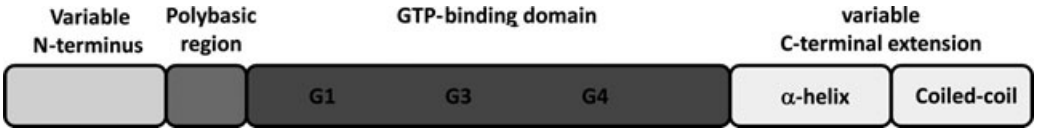

Fig. 2. General structure of septins. N- and C-termini vary between septin family members and their isoforms. Some septins contain a proline-rich domain in their amino terminus that is involved in protein interaction. The C-terminus of some septins consists of a coiled-coil domain predicted to contain an α-helix. The polybasic domain is responsible for the association of septins with the plasma membrane. The central GTP-binding domain contains conserved motifs G1 (GxxxxGK[S/T]), G3 (DxxG) and G4 (xKxD) and is implicated in the formation of septin heteroligomers and protein interaction.

the possible roles of these domains, as described later. Several members of the human septin family also contain the less well-studied proline-rich domain near the N-terminal region. Although there are no specific studies dedicated to understanding the functional role of the proline-rich domain of septins, one can hypothesize that this domain may be essential for protein–protein interactions, including interaction with proteins containing SH3 domains (3, 4). Preceding the GTPase domain, all mammalian septins, including human septins, contain a highly conserved polybasic domain responsible for the association of septins with cellular membranes. Studies of the polybasic domain of SEPT4 have shown that this domain binds to phosphoinositol phosphates (5). The polybasic domain might mediate the targeting of septins to membrane domains relevant for their role as diffusion barriers in yeast and mammalian cells. The Wittinghofer team studied the human septin complex composed of SEPT2, SEPT6 and SEPT7 and found that these three septins form a hexameric complex of two copies of each septin through a GTP/GDP bound interface, which is also crucial for the GTPase activity (6, 7). Future studies of these domains are necessary for comprehensive insight into septins' intricate functional roles in mammalian cells.

Septins are widely subjected to functionally significant post-translational modifications. For example, sumoylation of yeast septins in G2/M-arrested cells is well described, and the ubiquitin-protein ligase (E3) Siz1p is required for yeast septin sumoylation (8). Sumoylation of mammalian septins has not yet been reported. However, mammalian septins contain multiple phosphorylation sites and they can be phosphorylated by Ser/Thr kinases in post-mitotic neurons (9–11) and by Aurora B kinase in mitotic cells (12). This suggests that sumoylation and/or phosphorylation of septins might modulate conformational changes that can alter their functional role.

Functional role of septins

Despite the mechanistic differences between budding yeast and dividing animal cells (13), several orthologs of yeast septins were first identified in *Caenorhabditis elegans* (unc-59 and unc-61), *Drosophila melanogaster* (pnut) and mammals [SEPT2 (Nedd5) and SEPT4(H5)] (14–17). Similar to yeast septins, animal septins can form polymeric actin-associated filaments, hydrolyze GTP and produce multinucleated cells when mutated (18, 19). Septins can form microfilaments by interacting with each other or with cytoskeletal and filamentous proteins such as actin, myosin and tubulin, indicative of their functional roles in cytokinesis during contractile ring formation, cell morphology changes and dynamic scaffolds (14, 20–24). Several mammalian septins have many interacting partners (Table 2) and form complexes between family members to create filaments important in different cellular functions. One can speculate that some of the diverse functional roles of mammalian septins are intrinsically related to their physical interactions, which might explain how one septin can have multiple functions in different tissues and at different times during cell cycle and development.

In addition to their roles in cytokinesis, mammalian septins have been associated with other distinct cellular processes including vesicle trafficking, cell polarity, cytoskeletal dynamics, apoptosis, neurodegeneration and oncogenesis. The diversity and complexity of these septin-associated functions is not well understood, but it is believed that a wide range of hetero-oligomeric septin complexes are major players in these cellular processes. For example, *SEPT4/ARTS*, an alternative transcript of *SEPT4*, is translocated from the mitochondrion to the nucleus upon exposure to the apoptotic agent transforming growth factor-β (TGF-β), possibly providing a mechanistic link between cell division and cell death (25–27). Recent data indicate that several septins, including SEPT2, 4, 6 and 7, coprecipitate with the

Table 2. Representative interacting partners and functional roles of mammalian septins

Complexes	Putative functions	Implicated septin domain	References
SEPT1/Aurora B	Chromosome segregation, cytokinesis	Not determined	12
SEPT2/F-actin	Cytokinesis	GTP binding	14
SEPT2/5/6/anillin	Cytokinesis	Not determined	105
SEPT2/6/7	Filament formation	C- and N- termini	6
SEPT2/GLAST	Neurotransmitter release	Not determined	56
SEPT2/myosin II	Cytokinesis	Not determined	106
SEPT2/6/CENP-E	Chromosome segregation	Not determined	37
SEPT2/6/7/MAP4	Microtubule stability	Not determined	22
SEPT2/4/7/Sec6/8	Vesicle trafficking	Not determined	30
SEPT3/5/7	Neuronal biology	Not determined	107
SEPT4/5/8	Vesicle targeting/exocytosis	N- and C- termini	35
SEPT4/8	Platelet biology	Not determined	32
SEPT5/Parkin	Parkinson's pathogenesis	Not determined	50
SEPT5/11	Exocytosis in endothelial cells	GTP binding and C-terminal	33
SEPT5/SNARE complex	Vesicle targeting/exocytosis	GTP binding and C-terminal	28
SEPT6/12	Filament formation	Not determined	108
SEPT7/9/11/actin	Filament formation	N-terminal	109
SEPT7/CENP-E	Chromosome segregation	Not determined	48
SEPT8/Vamp2	Snare complex formation, neurotransmitter release	Not determined	55
SEPT9/actin	Stress fiber	Not determined	110, 20
SEPT9/SA-RhoGEF/actin	Rho signaling	N-terminal	110
SEPT9/HIF-1	Cell proliferation, angiogenesis, prostate cancer	N-terminus GTP binding	72, 96
SEPT9/JNK	Cell proliferation, breast cancer	GTP binding	100
SEPT9/tubulins	Filament formation, microtubules, spindle formation	GTP binding	20, 23, 24
SEPT11/12	Filament formation	Not determined	111
SEPT14/SEPT1-7/9/11-12	Testicular biology	Not determined	47

mammalian sec6/8 complex, suggesting an association of septins with membrane dynamics and vesicle trafficking (28–31). In addition, septins have been implicated in platelet function (SEPT4, 5 and 8) (32–35), cardiac myocyte development (36), chromosome dynamics (SEPT2) (37), cell polarity, motility and microtubule dynamics (SEPT9 and others) (20, 22–24, 38).

In a very elegant study, Kremer et al. showed that a complex of septin proteins (SEPT2, 6 and 7) interacts with SOCS7, which is necessary to retain SOCS7 and non-catalytic region of tyrosine kinase adaptor protein (NCK) in the cytoplasm at a steady state to regulate actin organization and the DNA damage response. The SOCS7/NCK complex accumulates in the nucleus to activate CHK2 and p53-mediated cell cycle arrest upon DNA damage. This action is potentiated by the depletion of the septin complex by siRNA. The spatial distribution of NCK as mediated by the septin complex is important in the reorganization of the actin cytoskeleton, cell polarity and the DNA damage response. One can predict that *in vivo* the distribution of septins in the cytoplasm is an important mechanism that regulates the localization of many proteins and their site of action in the cell (39).

SEPT2 and SEPT11 are required for phagosome formation, which is important for cell membrane dynamics (31). SEPT2 is also required for epithelial cell polarity by associating with tubulin networks and facilitating vesicle transport by preventing polyGlu microtubule tracts from binding to MAP4 (38). SEPT2 and SEPT11 are modulators of InlB-mediated invasion by *Listeria monocytogenes*. SEPT2 is essential for the entry of Listeria to the cells, but SEPT11 expression restricts the efficacy of Listeria invasion (44–46). SEPT12 has been implicated in mammalian spermatogenesis (40, 41). In addition, SEPT4 and SEPT7 serve as diagnostic markers for human male asthonozoospermia, because healthy individuals show septin expression in the annuli of spermatozoa while infertile patients do not (42). Ihara et al. showed that the expression of murine Sept4 is important for the cortical organization required for morphology and motility of the sperm flagellum (43). Overall, these findings show the diverse

roles of septins despite their high structural conservation.

Most recently, *SEPT14*, a novel testis-specific septin was identified and characterized as the newest member of the human septin family. This septin was identified in an effort to find novel interactors of SEPT9 isoforms using a yeast-two hybrid system. *SEPT14* maps to 7p11.2 in humans and includes a conserved GTPase domain and a carboxy-terminus coil-coiled domain characteristic of other septins. SEPT14 was found to interact with 10 other members of the human septins and localized with actin stress fibers, a general feature of septin filaments. Expression analyses in many fetal, adult and cancer tissues showed that *SEPT14* expression is limited to the normal testes by Northern blot and reverse transcription-polymerase chain reaction (RT-PCR). Interestingly, *SEPT14* expression was negative when tested in cancer cell lines isolated from testis (47).

Septins as microtubule-associated proteins

Several studies suggest that septins might be involved in microtubule dynamics and chromosome segregation. Two groups showed that mammalian SEPT2 and SEPT7 may form a mitotic scaffold for centromere protein E (CENP-E) and other effectors to coordinate chromosome segregation and cytokinesis (37, 48). Kremer et al. proposed a novel molecular function for septins in mammalian cells through the modulation of microtubule dynamics via an interaction with MAP4 (22). Looking specifically at SEPT9 isoforms, SEPT9_v1 MLL septin-like fusion gene variant A (MSFA) was found to localize specifically with microtubules. This localization was required for the completion of cytokinesis and it could be disrupted by nocodazole treatment (24). Interaction of SEPT9_v1 with microtubule networks was found to be essential for septin filament formation (23). We propose that there is a tight regulation between tubulin filaments, microtubules and septins filaments. How this regulation is mediated, and what other proteins are involved remains unclear. Fluorescence microscopy and further characterization of protein interactions might give better insight into septin–tubulin interaction and its regulation of chromosome segregation during mitosis.

Septins and neurological disorders

Possible roles for septins in neurological disorders have emerged based on the brain-specific expression of some septins (Table 3). SEPT2/NEDD5, SEPT1/DIFF6 and SEPT4/H5 have been found to associate with Alzheimer-specific neurofibrillary tangles (5, 49). The SEPT5/cell division control-related protein (CDCREL)-1 interaction with Parkin, a pathogenic protein in Parkinson's disease (50, 51), provides evidence for the involvement of another subset of septins in neuronal development and disease. SEPT4 has also been implicated in brain pathogenesis by its association with cytoplasmic inclusions in Parkinson's disease and other synocleinopathies (52). The SEPT3/5/7 complex was identified in the mammalian brain and SEPT3 specifically is developmentally regulated and enriched in presynaptic nerve terminals, suggesting a role for these septins in neuronal biology (53, 54). SEPT2 and SEPT8 are associated with neurotransmitter release due to their interaction with the glutamate transporter (Glast) and the synaptic vesicle protein synaptobrevin 2 (Vamp2), respectively (55, 56). Other septin complexes have been associated with myelin formation in the peripheral nervous system (57). Recently, *SEPT9* point mutations and a duplication within the gene have been identified in patients with the autosomal dominant neuropathy hereditary neuralgic amyotrophy (HNA) (58–60), further supporting a role for septins in neurological disease. The mechanism by which these mutations are pathogenic in HNA is still not fully elucidated, but McDade et al. showed that isoforms v4 and v4* have distinct 5′ ends encoded by exons where germline mutations of HNA are found. The two mRNAs are translated with different efficiencies and cellular stress can alter this pattern (61). These mutations dramatically enhance the translational efficiency of the v4 variant, leading to elevated SEPT9_v4 protein under hypoxic conditions (61). These data provide mechanistic insight into the effect of HNA mutations on fine control of SEPT9_v4 protein and its regulation under physiologically relevant conditions. The data are consistent with the episodic and stress-induced nature of the clinical features of HNA (61).

Septins in cancer

The first evidence that septins may contribute to neoplasia occurred with the discovery of septin *SEPT5/CDCREL-1* as a carboxy-terminus fusion partner with mixed lineage leukemia (MLL) in an acute myeloid leukemia (AML) patient with a t(11;22)(q23;q11.2) translocation (62). Subsequently, *SEPT9/MSF*, *SEPT6*, *SEPT2*, and *SEPT11* were also identified as fusion partners with MLL in human leukemic cells (63–66). *MLL*, the human homolog of Drosophila trithorax, is a

Table 3. Characteristics of human septin loci and disease associations

Human septin	Alternative names	Human chromosome location	Expression	Disease associations
SEPT1	*DIFF6*	16p11.1	Brain, lymphocytes, others	Alzheimer's disease, leukemia, lymphoma
SEPT2	*NEDD5, DIFF6*	2q37	Brain, lymphocytes, others	Brain, liver and renal cancer, Von Hippel-Lindau syndrome, Alzheimer's disease, Shigella and Listeria infections
SEPT3	*SEP3, G-SEPTIN*	22q13.2	Brain-specific	Brain cancer, Alzheimer's disease
SEPT4	*ARTS, H5, PNUTL2, BRADEION, SEP4*	17q22	Brain, testes, eye, lymphocytes	Alzheimer's disease, skin, urogenital and colon cancer, leukemia, male infertility (spermatogenesis defect)
SEPT5	*CDCREL-1, PNUTL1*	22q11.21	Brain, eye, platelets	Leukemia, Parkinson's disease, schizophrenia, pancreatic cancer
SEPT6	*SEP2, KIAA0128*	Xq24	Ubiquitous	Schizophrenia, leukemia, hepatitis C
SEPT7	*CDC10*	7q36.1	Brain, testes	Nervous system cancers, male infertility (spermatogenesis defect)
SEPT8	*KIAA0202*	5q31	Brain, retina and others	Retinal degeneration
SEPT9	*MSF, PNUTL4, AF17Q25, OvBrSEPT, SINT1, KIAA0991*	17q25	Ubiquitous	Hereditary neuralgic amyotrophy, leukemia, breast, ovarian and colorectal cancers, head and neck cancers, classical Hodgkin lymphoma, Shigella and Listeria infections
SEPT10	*SEPT1-like*	2q13	Ubiquitous	–
SEPT11	*FLI10849*	4q21.1	Ubiquitous	Schizophrenia, bipolar disorder, leukemia, Shigella and Listeria infections
SEPT12	*FLI25410*	16p13.3	Lymphocytes, testes	Male infertility (spermatogenesis defect)
SEPT13	–	7p13	Ubiquitous	–
SEPT14	–	7q11	Testes	–

common translocation partner in leukemias with more than 80 rearrangements with 50 fusion partners identified (67). The well-characterized MLL fusion products produce in-frame translated chimeric proteins associated with phenotypic disease variability such as leukemia type and prognostic outcome. These carboxy partners, in addition to MLL, appear to be essential contributors to the pathogenesis of leukemia (68).

Five human septins have also been implicated in other types of cancer including SEPT2, SEPT3, SEPT4, SEPT5 and SEPT9 (25, 69, 70). In fact, SEPT4 acts as a tumor suppressor in leukemias and solid tumors. The *SEPT4* gene promotes apoptosis, and is lost in 70% of leukemia patients (26), in addition to being associated with inhibition of colorectal cancer tumorigenesis (71). SEPT9 seems to be important not only in leukemias but also in solid tumor cancers (72–77). SEPT2 and SEPT3 were abundantly expressed in several brain tumors and brain tumor cell lines, suggesting that these family members are potential oncogenes (70). SEPT2 phosphorylation by casein kinase 2 was found to be important for hepatoma carcinoma cell proliferation (78). In addition, SEPT2 is the only human septin that has been associated with a specific human cancer predisposition syndrome, Von Hippel-Lindau (VHL). VHL is an autosomal dominant genetic condition characterized by hemangioblastomas in different tissues and renal cell carcinoma. Increased SEPT2 expression is a common event in renal cell carcinomas (78, 79). A proteomic study by Craven et al. showed that SEPT2 was downregulated upon expression of VHL in the UMRC2 renal cell carcinoma line. This suggests that SEPT2 is subject to either direct or indirect VHL regulation (78, 79).

Overall, these studies show that human septins are important in many cellular and molecular functions, as summarized in Fig. 3. It seems that their expression needs to be highly regulated and the dynamics with their interaction partners are crucial for their function as either scaffolds for cytoskeletal proteins or signaling GTPases. Mutations or altered expression of these genes can arise by multiple mechanisms that are not well understood. Many septins are strikingly associated with multiple human diseases, primarily cancers and neurological disorders (Table 3 and Fig. 3).

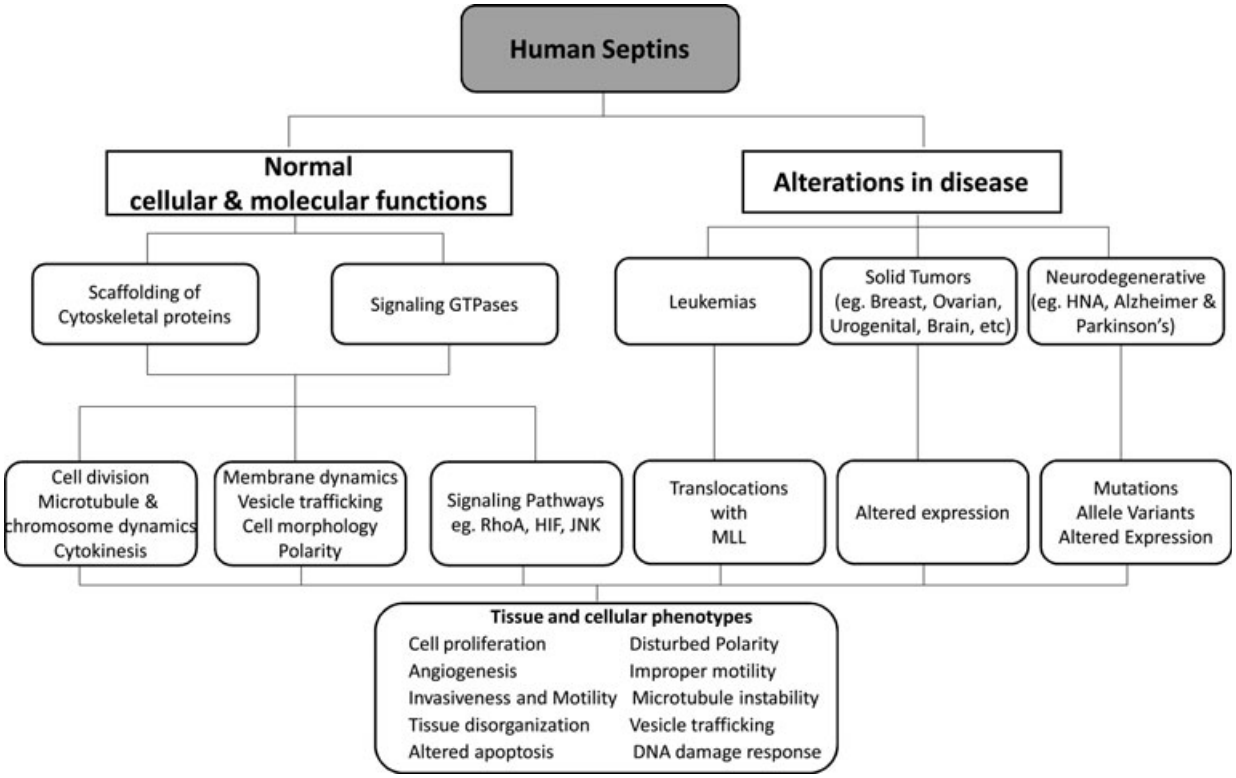

Fig. 3. Human septins in health and disease. Human septins are involved in multiple tissue and cellular phenotypes. Alterations in their expression or gene mutations affect these phenotypes, which are mechanistically important in the pathogenesis of many diseases such as neurological diseases and cancer.

Human *SEPT9* locus

SEPT9, with demonstrated roles in both cancer and neurological disease, provides an illustration of the diversity of human septin loci. Human SEPT9 became of great interest to the septin scientific community after it was found to be an *MLL* translocation partner in leukemia (66). Subsequently, *SEPT9* was mapped to chromosome 17q25, a region linked to breast and ovarian cancers, by positional cloning to a region of allelic imbalance in breast and ovarian cancers (74, 80–82). This suggested that alterations of this novel septin gene may be important not only in leukemia but also in breast and ovarian cancers. Afterward, it was shown that the *SEPT9* locus gives rise to multiple alternative transcripts encoding at least seven annotated isoforms (SEPT9_v1-SEPT9_v7) (74). The *SEPT9* locus contains 13 exons and shows high variability at the 5′ and 3′ ends by either alternative splicing of exons or different transcription start sites. The variable exons 1–3 and 12–13 encode alternative translational start and stop sequences and are spliced onto a core of eight coding exons (Fig. 4) (74). These isoforms maintain the general structure of septins with a highly conserved central region containing the polybasic domain and GTP-binding domain (Fig. 2). They vary in the 5′- and 3′-UTRs and at the N- and C-terminus of the protein. Interestingly, the SEPT9_v4 and SEPT9_v4* isoforms encode for the exact same protein, but they differ at their 5′-UTRs, suggesting that these transcripts might be differentially regulated in time or tissue of expression (73, 76, 77). *SEPT9_v1* and *SEPT9_v3*, the longest transcripts, are highly similar except for 25 distinct amino acids at the N-terminus of SEPT9_v1. The biological reason for the presence of multiple *SEPT9* transcripts is still not elucidated, but many studies, including expression analyses, show that these isoforms are differentially expressed and may have distinct functional roles in mammalian cells.

SEPT9 is widely expressed based on ubiquitous adult and fetal transcript expression, although individual isoforms may have tissue-specific expression (74). The cellular localization of SEPT9 isoforms is largely cytoplasmic in interphase cells, but the SEPT9_v1 isoform has a bipartite nuclear localization signal that may direct the shuttling of SEPT9_v1 between the nucleus and the cytoplasm. In mitotic cells, SEPT9 exhibits a punctate staining pattern located between the separating

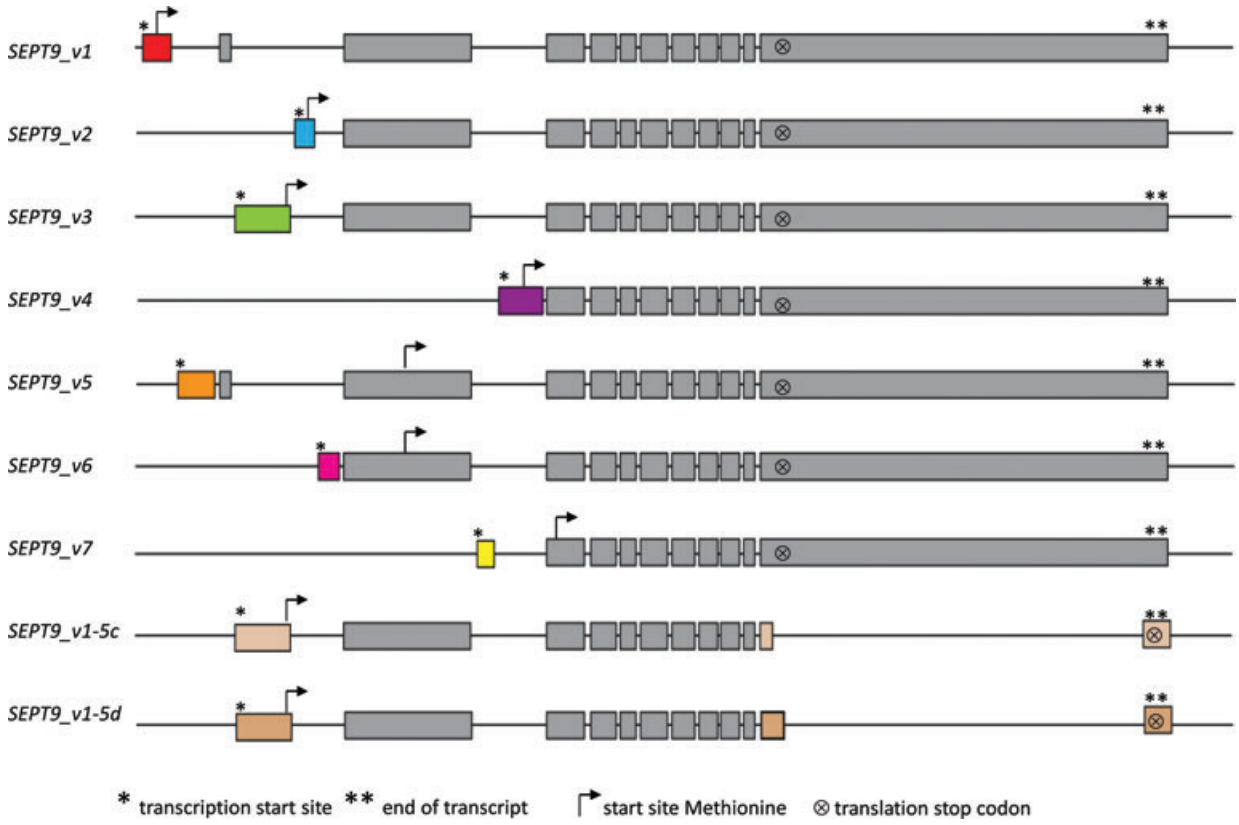

Fig. 4. SEPT9 genomic structure. Genomic structure of SEPT9 alternatively spliced transcripts and variants. *SEPT9* exhibits 5′ and 3′ alternative spliced and variable exons and is composed of 13 exons in total. Gray boxes indicate common exons and colored boxes indicate variant-specific exons, all drawn to scale. Transcriptional start sites are indicated by (*) and the end of each transcript by (**). The variable exons (colored boxes) encode different translational start (arrow) and stop (⊗) sequences and are spliced into a core of common coding exons shared between variants (gray boxes).

chromosomes and at the cleavage furrow during telophase (24). SEPT9_v1 is localized to microtubule networks in interphase cells and in mitotic cells it is localized at the mitotic spindle and the bundle of microtubules at the midzone (23). Both studies showed that when SEPT9 is ablated, cells become binucleated, suggesting a role for SEPT9 in cell division via interaction with components of the cytoskeleton such as tubulins.

Since they were discovered, septins had been characterized as cytoskeletal GTPases important in cell division. Mutations of this family of genes in yeast lead to budding defects, cell cycle arrest and cytokinesis defects. In mammals, several septins (e.g. SEPT2, SEPT5, SEPT7) also have been implicated in mitosis, specifically in chromosome segregation dynamics and cytokinesis (Table 2). SEPT9 is not an exception. Its localization to microtubules, the cleavage furrow and midbody at different stages in mitosis suggests a possible specific role of SEPT9 isoforms in chromosome segregation and/or completion of cell division by affecting the mitotic spindle assembly, disassembly or dynamics and the cytokinesis process (Fig. 5).

Intricate human SEPT9 nomenclature

Human septin nomenclature has evolved on the past decade as illustrated by many alternative names as shown in Table 3, making the septin literature difficult to reconcile. *SEPT9* is no exception, as it was originally called MLL septin-like fusion (MSF) due to the fact that it was identified as a fusion partner of MLL in leukemias (66). In 2002, a committee of septin researchers developed an official nomenclature system for *SEPT9* transcripts (83). This new name was derived from the functional role of these genes in septae formation in yeast. Some research groups published with the old nomenclature while others used their own versions, making progress in SEPT9 research hard to reconcile. New nomenclature was established by the National Center for Biotechnology Information (NCBI) and HUGO Gene Nomenclature Committee (HGNC), but it has yet

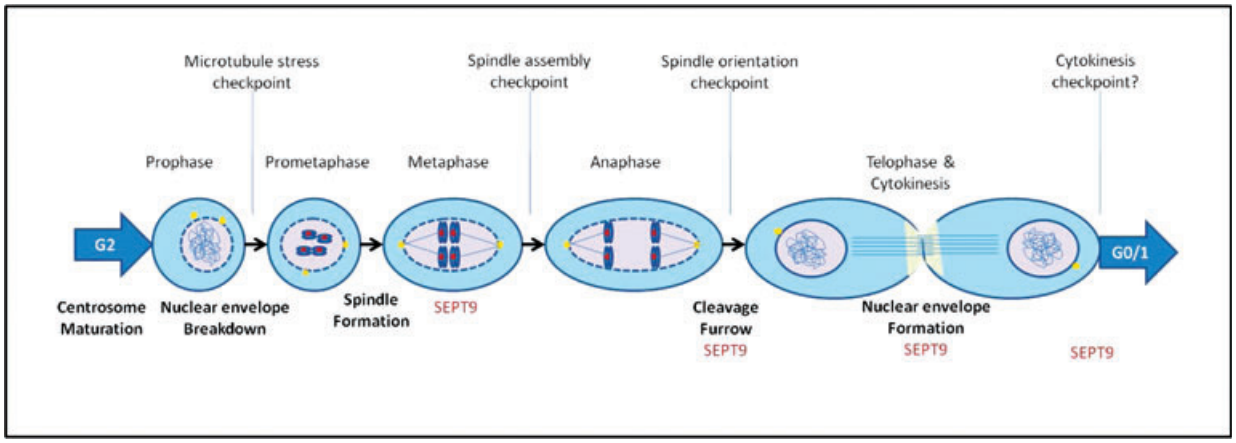

Fig. 5. SEPT9 functional role in mitosis. Diagram showing the phases in mitosis in which SEPT9 expression is present. SEPT9 is localized to the microtubules at the midzone during anaphase and at the cleavage furrow in telophase. Its particular localization during mitosis suggests a role in chromosome segregation and cytokinesis.

to be universally accepted by the septin community. These nomenclature changes are depicted in Table 4 by group and year. Throughout this review the nomenclature utilized was established in 2005 by Scott et al. and endorsed at the 2009 International Septin Meeting (76).

SEPT9 as a translocation partner of MLL in leukemia

Originally, SEPT9/MSF was identified as part of a fusion protein with the myeloid/lymphoid leukemia gene (MLL) in a therapy-induced acute myeloid leukemia (t-AML) patient with a t(11;17)(q23;q25) rearrangement and was named MSF (66). The translocation codes for an in-frame transcript joining the 5′ of MLL through exon 5 to *SEPT9* at the start of exon 3 through the 3′ terminus. A reciprocal transcript was amplified in one patient joining the 5′ of MSF through exons 1-7 of *MLL* but was out of frame (66, 84). The fusion protein was composed of the amino protein terminus of MLL, including the nuclear localization signal, the A-T hook DNA binding domain, and the DNA methyltransferase-like DNA binding domain, and a carboxy terminus of SEPT9_v1, including the proline-rich domain, the polybasic and GTPase domains. Lost from the carboxy terminus of MLL is the PHD zinc finger protein–protein interaction domain and the SET domain thought to regulate gene expression through chromatin remodeling (66, 84). It has been suggested that MLL is the sole clinical cause in leukemias with 11q23 rearrangements as it is fused to a wide variety of other genes. However, all of the well-characterized MLL fusion products produce in-frame translated chimeric proteins associated with phenotypic disease variability such as leukemia type and prognostic outcome, which provide further evidence that proteins at the varying reciprocally translocated chromosomes are essential contributors to the pathogenesis of leukemia (67, 68, 85). Thus, speculation on the contributions of MLL-SEPT9 fusion protein expression to haematopoetic cellular transformation would include potential mislocalization of SEPT9/MSF from the cytoplasm to the nucleus, aberrant expression of MLL target proteins and altered activation of MSF GTPase signaling pathways. This suggests that these carboxy partners, in addition to MLL, are essential contributors to the pathogenesis of leukemia (68) and implicates septin family members in oncogenesis (85).

SEPT9 model of oncogenesis in solid tumors

A compelling example of the role of septins in the oncogenesis of solid tumors was the identification of the MSF/SEPT9 murine ortholog Sint1/Sept9 at a provirus insertion site in SL3-3 murine leukemia virus (MLV)-induced lymphomas (86), which demonstrated that this septin locus is a site for oncogenic integration. *SEPT9* also maps to a region of allelic imbalance at chromosome 17q25.3 in breast cancer (74) and sporadic ovarian cancer (82). In addition, there is a differential expression of SEPT9 isoforms in tumors of various tissues (21, 77, 87, 88). SEPT9 has been characterized as a candidate gene in head and neck squamous cell carcinomas by a genome-wide screen for methylated genes (89, 90). SEPT9 was also identified as a possible candidate gene for classical Hodgkin lymphoma (cHL) (91). Circulating methylated *SEPT9* DNA in plasma was recently

Table 4. Human SEPT9 nomenclature

Kalikin et al. (2000)	McIlhatton et al. (2001)	Macara et al. (2002)	Nagata et al. (2004)	Scott et al. (2005)[a]	NCBI (2008)	HGNC (2008)	NCBI accession numbers
					Variant/isoform	Isoform	Transcript/protein
MSF-A	Epsilon	*SEPT9_v1*	SEPT9a	*SEPT9_v1a*	*SEPT9_v1*/SEPT9a	SEPT9_i1	NM_001113491/NP_001106963
–	Gamma	–	–	*SEPT9_v2a*	*SEPT9_v2*/SEPT9b	SEPT9_i2	NM_001113493/NP_001106965
MSF	Alpha	*SEPT9*	SEPT9b	*SEPT9_v3a*	*SEPT9_v3*/SEPT9c	SEPT9_i3	NM_006640/NP_006631
–	–	–	–	–	*SEPT9_v4*/SEPT9d	SEPT9_i4	NM_001113495/NP_001106967
MSF-B	Zeta	*SEPT9_v2*	SEPT9c	*SEPT9_v4**a	*SEPT9_v5*/SEPT9e[c]	SEPT9_i5	NM_001113492/NP_001106966
MSF-C	Beta	*SEPT9_v3*	SEPT9c	*SEPT9_v4a*	*SEPT9_v6*/SEPT9e[c]	SEPT9_i6	NM_001113494/NP_001106966
–	Delta	*SEPT9_v4*	–	*SEPT9_v5a*	*SEPT9_v7*/SEPT9f	SEPT9_i7	NM_001113496/NP_001106968
–	–	*SEPT9_v5*	–	*SEPT9_v1-5b-c*[b]	–	–	–

MSF, MLL septin-like fusion.

[a]Current nomenclature in peer-reviewed publications.

[b]SEPT9_v1-5b-c variants differ at the 3′-UTR. Not well characterized.

[c]SEPT9 variants 5 and 6 differ in their 5′-UTR but encode the same protein isoform.

identified as a valuable biomarker for minimally invasive detection of colorectal cancer. This led to the development of a new methylation (m)SEPT9 assay that may prove useful in clinical research for the detection of invasive colorectal cancer with a simple blood test from patients (92–94).

Finally, an isoform of SEPT9, SEPT9_v1, might be important as a biomarker for therapeutic resistance of many cancers to microtubule disrupting agents. SEPT9_v1 expression was strongly correlated with susceptibility of a wide range of cancer cells to drugs such as paclitaxel (95). In general, cancer cells with high SEPT9_v1 expression were more resistant to these drugs (95).

SEPT9 isoforms have been associated with signaling pathways relevant to oncogenesis. For example, SEPT9_v1 interacts with hypoxia inducible factor-1-alpha (HIF-1-α) preventing its ubiquitination and degradation, thereby activating HIF downstream survival genes to promote tumor progression and angiogenesis in prostate cancer cells (72). Also, a new study showed that SEPT9 upregulates HIF-1 by preventing Rack1-mediated degradation in an oxygen-independent manner (96). In addition, a gene expression profile of prostate cancer showed that SEPT9 was overexpressed in tumors with chromosomal fusion between androgen-regulated transmembrane protease serine 2 (TMPRSS2) and v-ets erythroblastosis virus E26 oncogene (ERG). This fusion is associated with a more aggressive clinical phenotype and tumors with TMPRSS2-ERG are regulated by a estrogen-dependent signaling and are considered a distinct molecular subclass (97). The SEPT9_v3 isoform binds SA-RhoGEF, functioning as a scaffold to keep it in an inactive state, thereby inhibiting SA-RhoGEF-mediated Rho activation (98, 99). This finding was crucial for the study of septins in cancer because it provided a direct link between septins and signaling proteins involved in cellular functions such as actin cytoskeletal organization, transcriptional activation, tumor invasion, cell morphology, cell motility and cytokinesis.

SEPT9 expression is also altered in many types of cancers including head and neck tumors, ovarian, prostate, and breast cancers and it is overexpressed in a mouse mammary tumor virus (MMTV) mouse model of mammary tumorigenesis (20, 72–76, 86, 92). Most recently, Gonzalez et al. showed that preferential expression of SEPT9_v1 in human mammary epithelial cells promotes pro-oncogenic phenotypes. Briefly, ectopic expression of *SEPT9_v1* using retroviral constructs in two immortalized human mammary epithelial cells, MCF10A and HPV 4-12, increases cell proliferation, decreases apoptotic response and

enhances motility and invasiveness, in addition to present a reminiscent of epithelial to mesenchymal transition (EMT), all hallmarks of oncogenic transformation in epithelial tissues. In addition, knockdown of *SEPT9*, and specifically *SEPT9*_v1, via RNA interference assays in two cancer cell lines with high endogenous levels of *SEPT9*_*v*1 (MDA-MB-231 and BT-549) complemented the observations made in the expression model by rescuing tumorigenic phenotypes. Another striking phenotype found was that high SEPT9_v1 expression disrupts proper formation of tubulin microfilaments in interphase cells and increases aneuploidy. This study provides compelling evidence that SEPT9_v1 could drive malignant progression in mammary epithelial cells (20). Another study also by Gonzalez et al. demonstrated that upregulation of SEPT9_v1 might increase proliferation rates of mammary epithelial cells by stabilizing c-Jun-N-terminal kinase (JNK) proteins, which are involved in cell proliferation and cell cycle progression. High SEPT9_v1 expression also showed to increase JNK kinase activity and the transcriptional activation of JNK target genes important in cell cycle progression, including cyclin D1 (100).

As a result of these studies, SEPT9 is now accepted as a novel cancer-associated protein and is emerging as a potential biomarker for diagnosis and chemotherapeutic response in some epithelial cancers.

Conclusion

Since septins were discovered almost 40 years ago, septin research has grown impressively, from four genes identified in budding yeast in the mid-1970s to 14 members identified in humans today. In yeast, septins were primarily described as filamentous proteins necessary for budding morphology and cell cycle progression by possibly interacting with cytoskeleton components. The variety of septin isoforms and the significant diversity of their functions in eukaryotic cells have proven to be intriguing and exciting. Studies of mammalian septins have been primarily focused on their association with cancer and neurological diseases. However, many other interesting functions are coming to light such as the role of certain septins in bacterial infection (44–46), angiogenesis (72), spermatogenesis (40–43, 101), retinal degeneration (102, 103), platelet release reaction (32–35, 104), and beyond. Still, questions related to their normal function in cells and to their implication in human diseases are still puzzling. Major fundamental questions still need to be studied including but not limited to: which factors regulate the tissue-specific and temporal-specific expression of these proteins?, why do human cells need the presence of 14 distinct septins?, or which molecular and/or cellular alterations dictate the involvement of each specific septin in human diseases? Still, many of the contributions in septin biology in the last years including the first crystal structure of septin oligomers, additional protein interactions, expression profiles and associations with signaling pathways and human diseases have set the path to more exciting experimental strategies to understand further their role in sickness and in health.

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Conflict of interest

The authors declare that no conflict of interest exists.

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