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1 **Septins in animal tissue architecture: more than just peanuts**

2
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8 9 **Abstract**

10 Septins are cytoskeletal GTP-binding proteins that were discovered in budding yeast
11 and are conserved from algae and protists to mammals. Septins assemble into
12 heteromeric complexes, which can polymerize into filaments and higher-order filament
13 architectures, and perform functions in a wide range of biological processes, including
14 cell division and motility and tissue morphogenesis. Although septin dysfunction in
15 animals is linked to infertility, defective organogenesis, neurodegenerative diseases
16 and cancer, the molecular mechanisms underlying septin function are not clear.
17 Studies of septins *in vivo* in whole animals provide a powerful approach for gaining
18 insights into the role of septins in animal pathophysiology and unraveling the molecular
19 and cell biological basis of septin function.
20

21 **Introduction**

22 Septins are conserved cytoskeletal GTP-binding proteins [1] with roles in diverse
23 biological processes, from cell division and sperm integrity to host-pathogen
24 interactions [2], and in human pathophysiology [3]. The embryonic lethality of septin-
25 depleted mice and *Drosophila* [4-7] highlights their essential contribution to animal
26 physiology, yet the molecular basis of septin function remains unclear.

27 Septins assemble and function as heteromeric complexes [8] (Figure 1) which are
28 thought to polymerize into filaments and higher-order filament assemblies. Studies
29 using cultured cells provide unprecedented insights into septin biology, however
30 understanding how septins contribute to animal physiology necessitates their
31 complementary study *in vivo* in whole animals. This review focuses on *in vivo* studies
32 of septin function in tissue architecture using the established invertebrate (*C. elegans*,
33 *Drosophila*) and vertebrate (mouse, zebrafish, *Xenopus*) animal model systems. We
34 review septin functions in dividing embryos and tissues and in nondividing tissues and
35 discuss the molecular mechanisms underlying septin function.
36

37 **Animal septins in dividing embryos and tissues**

38 The seminal article of Neufeld and Rubin was the first to report in *Drosophila* the
39 localization of animal septins to the cytokinetic cleavage furrow and to intercellular
40 bridges connecting daughter cells in dividing tissues [9]. Growing imaginal discs - the
41 precursors of adult tissues- depleted of the *Drosophila* septin Peanut (*Pnut*, Figure 1)
42 failed to proliferate, and contained multinucleate cells, consistent with a requirement
43 of septins in cytokinesis [9]. The *Drosophila* septins *Sep2* and *Sep5* were later shown
44 to have redundant roles in imaginal disc proliferation, with double *sep2 sep5* null
45 mutants lacking imaginal discs similar to *pnut* mutants [10]. Similar proliferation

46 defects linked to cytokinesis failure were observed in septin mutant ovarian follicle
47 cells [9-11]. The roles of septins in dividing embryos and tissues have been studied in
48 particular in *Drosophila* and *C.elegans* and are reviewed in the following sections for
49 the respective model systems.

50

51 ***Drosophila* syncytial blastoderm embryo**

52 In the *Drosophila* syncytial blastoderm, nuclei at the embryo periphery divide four
53 times before membrane invagination separates them to form the primary epithelium of
54 the embryo (cellularization). Coincident with each nuclear division cycle are transient
55 membrane invaginations, called metaphase furrows (MFs), which are crucial for
56 separating mitotic spindles. Septins localize to the cortical region above and in
57 between interphase nuclei, as well as along MFs and enriching at their tips [12,13].
58 Septin, and the septin-interacting protein, Anillin, are lost from the interphase cortex
59 in embryos depleted from the formin Diaphanous (Dia) [14]. Septin recruitment to the
60 MFs is regulated by the Ran pathway through the binding of importin to Anillin, which
61 blocks Anillin-Pnut interaction [15]. In the absence of Pnut, MFs are short-lived and
62 ingress much less [15,16], suggesting that Pnut promotes furrow stability and
63 ingression. Pnut recruitment to MFs was further shown to depend on dynamin,
64 syndapin and Par3/Bazooka [16-18].

65

66 ***Drosophila* embryo cellularization**

67 Septins localize to the tips of invaginating membranes (cleavage furrow tips) during
68 cellularization, colocalizing with the constricting actomyosin ring [9,12,19-21]. Septin-
69 depleted embryos succeed to cellularize, however membrane ingression is slower, the
70 membrane fronts constrict irregularly, actomyosin accumulation is not timely and
71 myosin levels are reduced. Additionally, actomyosin does not form rings but
72 concentrates in bars and becomes progressively diffuse [7,21] (Figure 2A). The actin
73 filament cross-linking and -bending capacity of septins was suggested to contribute to
74 the optimal organization of actin filaments in the actomyosin ring [21], in line with the
75 role of septins in controlling the timely transition from the slow to the fast phase of the
76 constriction [19]. Septins localize not only to the cleavage furrow tips but also to tubular
77 extensions emanating from those tips whose formation depends on dynamin and
78 amphiphysin and impacts timely ingression [20], raising the possibility that septins
79 contribute to local membrane remodeling. Septin recruitment to the cleavage furrow
80 tips depends on Anillin which binds septins through its PH domain [22]. The
81 stabilization of Anillin at the membrane is reciprocally dependent on septins [7,22].

82

83 ***Drosophila* pupal epithelial tissues**

84 Septins are required for planar cytokinesis in pupal epithelial cells [23,24]. Although
85 septins are dispensable for asymmetric furrowing [23], their depletion reduces the
86 constriction rate of the contractile actomyosin ring [23,24], reduces adherens junction
87 (AJ) recoil velocities upon ablation [24] and leads to cytokinesis failure and
88 binucleation [23,24]. Myosin-II in the septin-depleted rings is unchanged whereas
89 Anillin is significantly reduced [23]. The formation of new AJs between daughter cells

90 requires the disengagement of E-cadherin (E-cad) complexes between mitotic and
91 neighboring cells at the cleavage furrow, followed by *de novo* assembly of E-cad
92 complexes at the daughter-daughter cell interface. Septin disruption prevents this
93 process and leads to defective AJ remodeling. E-cad at the ingressing membrane of
94 dividing cells is either not reduced [23,24], or reduced only on one side leading
95 respectively to no new junction formation, or formation of a new junction only on one
96 side which seems to break apart: the constricting ring seems to detach or disassemble
97 in either case leading to membrane regression and binucleation [23,24] (Figure 2B).
98 The work from these studies suggests a tension-based mechanism whereby septins
99 in the contractile actomyosin ring are required for the ring to be able to exert sufficient
100 pulling forces against the AJ-mediated adhesion with neighboring cells to allow for
101 proper AJ remodeling [23,24].

102

103 **C. elegans embryo**

104 Septins were shown to localize to the ingressing furrow and enrich in the cytokinetic
105 ring of the dividing 1-cell *C.elegans* embryo (zygote) [25-27]. Although postembryonic
106 divisions fail variably in septin mutants [25], septins are not required for embryonic cell
107 divisions [25,26]. Cleavage furrow ingression in the zygote is asymmetric and reflects
108 the structural asymmetry of the contractile ring with septins, Anillin and actomyosin
109 coalescing on the side of the ring that ingresses the fastest [26]. This asymmetry
110 requires septins [26]: in the septin-depleted embryo, the cleavage furrow ingression
111 rate is unchanged [26,27], however furrowing becomes symmetric and cytokinesis
112 becomes sensitive to inhibitors of contractility [26]. Septins were proposed to serve a
113 mechanical function to make cytokinesis robust to mechanical challenges. The fact
114 that septins in the *C.elegans* embryo are required for asymmetric furrowing but not for
115 cytokinesis, whereas septins in *Drosophila* epithelia require septins for cytokinesis but
116 not for asymmetric furrowing might reflect differences in cell-cell adhesion, which
117 might provide a more sensitized context for septin function in the case of *Drosophila*
118 epithelia.

119 Septin recruitment to the cytokinetic ring of the zygote depends on Anillin [28]. Septins
120 also enrich in the anterior cortex of the zygote [27,28] in a cortical PAR protein-
121 dependent manner [27] but are dispensable for anterior-posterior polarity [27]. More
122 recently, septins were also shown to be required for chiral cortical rotation [29,30],
123 either by polarizing formin distribution or/and cross-linking different actomyosin bundle
124 populations.

125

126 **Animal septins in nondividing tissues**

127 The seminal work of Fares and colleagues in *Drosophila* was the first to report
128 localizations of septins not related to cytokinesis [12]. Septins concentrated at the
129 leading edge of the migrating epithelium during dorsal closure in the embryo and at
130 the cortices of amnioserosa cells [12]. In other tissues, septins localized to the
131 basolateral surfaces of ovarian follicle cells, to the plasma membrane of migrating
132 border cells, as well as to neurons of the embryonic central nervous system, the latter
133 also reported by Neufeld and Rubin [9]. The following sections review roles of septins

134 in nondividing tissues, notably on collective cell rearrangements, ciliogenesis, and
135 overall tissue architecture.

136

137 **Collective cell rearrangements**

138 Work in *C.elegans* was the first to report septin roles in cellular and axonal migration
139 [31]. Septins are expressed in the developing nervous system, with septin depletion
140 leading to fewer ventral cord motor neurons and defective axon guidance. Septins
141 were also present in distal tip cells, which are leaders for gonad arm extension. Septin
142 disruption affected their morphology, increasing the number and length of membrane
143 extensions, and impaired their migration and guidance [31].

144 Septins were later shown to contribute to the convergent extension of mesenchyme
145 cells in the *Xenopus* embryo. Using explanted gastrula tissues, Kim and colleagues
146 reported that septin-depleted tissues showed a reduced elongation of cells along the
147 convergence axis and an overall reduced convergent extension [32] (Figure 2C). The
148 Planar Cell Polarity (PCP) proteins Fritz and Dishevelled (Xdd1) were shown to control
149 septin recruitment, as the cortical and vertex localization of septins was lost upon their
150 depletion [32,33]. Strikingly, septin-depleted tissues showed undulating plasma
151 membranes with rapidly forming and resolving intercellular gaps (Figure 2C). This
152 same phenotype was also observed in Fritz-depleted mucociliary epithelia where Fritz
153 similarly controls cortical septin recruitment [34]. Shindo and Wallingford showed
154 additionally that septin depletion disrupted actin enrichment and compartmentalization
155 at vertices, abolished the planar polarization of phospho-myosin-II along the
156 convergence axis and reduced the difference in recoil velocities between shrinking
157 and extending junctions upon ablation [33]. These studies proposed that septins
158 compartmentalize cortical actomyosin to direct the shrinkage junctions for proper
159 convergent extension. Recent work showed that yet another PCP protein, Vangl2, was
160 important for septin recruitment, but that septins were also required for its proper
161 polarization [35]. Septin depletion also led to defective neural crest cell migration in
162 *Xenopus* embryos [36].

163 Recent work further showcased the requirement of septins for border cell migration in
164 the *Drosophila* female germline [37]. Septins are enriched at membranes between
165 border cells and nurse cells. Border cells first round up and then delaminate before
166 migrating in between nurse cells toward the oocyte. However, upon septin depletion,
167 delamination was impaired and of those clusters that detached, many failed to migrate
168 normally. Whereas a single leader cell forms protrusions in wild type, septin-depleted
169 clusters had ectopic protrusions and overall much higher shape variability (Figure 2D).
170 Importantly, although septin and myosin-II signals correlate dynamically during border
171 cell migration, active Rho was shown to independently recruit septins and myosin-II to
172 border cell membranes [37]. Septins were similarly shown to be targeted to the
173 cytokinetic ring of the dividing *C.elegans* zygote independently of myosin-II [28].

174

175 **Ciliogenesis**

176 In *Xenopus*, septins are found at the bases of cilia, with septin loss leading to fewer
177 and shorter cilia and defective Hedgehog signaling [32]. Further, in zebrafish,

178 depletion of septins led to fewer and shorter cilia in pronephric epithelial cells and in
179 Kupffer's vesicle, misorientation of basal bodies and cilia and defects in fluid flow and
180 thus to abnormalities in left-right asymmetry, compromising left-right patterning of
181 internal organs, the overall defects resembling human ciliopathies (Figure 2E) [38,39].
182 Ciliogenesis was also compromised in the photoreceptor outer segments [39] as well
183 as in the neural tube with defective Shh signaling [38]. Septins localized at the base
184 of cilia or along their axonemes [38,39].

185

186 **Tissue morphogenesis and architecture**

187 Septins were first shown to be essential for epithelial tissue architecture in the
188 *Drosophila* gastrulating embryo. After cellularization, septin localization persists at the
189 bases of the formed cells in cytoplasmic connections between the latter and the
190 underlying yolk (yolk plugs) [9]. Peanut-depleted embryos presented dramatic defects,
191 including the opening of cell bases, ectopic folds, widespread disruption of cell integrity
192 and delayed tissue extension [7].

193 Septins were further shown to have roles in the *Drosophila* germline. *Sep2* has a
194 unique function in follicle cell encapsulation during oogenesis, with *sep2* mutant
195 females, but not *sep5* mutant ones, being semisterile [10,40]. *sep2* null egg chambers
196 have abnormal numbers of nurse cells and oocytes, resulting from fusion of multiple
197 cysts into a single egg chamber [10,40]. *sep2* mutant males are sterile [40]. In
198 proliferating germline cells, septins enrich at the cortex and cytokinetic furrows, and
199 septins remain cortical throughout oogenesis, persisting at ring canals [40], which are
200 arrested cleavage furrows bridging the cytoplasm of nurse cells and the oocyte.
201 Septins similarly enrich at ring canals in the male germline [40,41]. Septins localize to
202 the outer rim of ring canals and also form transiently double rings both in the male and
203 female germline [40], possibly related to midbody remodeling that was recently shown
204 to precede ring canal formation [42]. Despite septin enrichment at cytokinetic furrows
205 and ring canals, septin null female germline clones do not show defects in cell number
206 or ring canal formation and can develop into eggs, suggesting that septins are not
207 essential for female germline cell divisions [7,40].

208 Recent work further highlighted the importance of septins for germline extension, the
209 maintenance of its syncytial architecture and production of oocytes in *C.elegans* [43].
210 It is notable that septin mutant phenotypes included irregular compartment sizes, as
211 well as irregular and vesiculated compartment and oocyte plasma membranes [43]
212 pointing to defects in membrane integrity (Figure 2F). Septins localize to the oocyte
213 plasma membrane and to the rachis lining, enriching in rachis bridges [25,43,44],
214 which are cytoplasmic connections between the germ cell compartments and the
215 common central cytoplasm (rachis) and were recently shown to contain a contractile
216 actomyosin corset, a structure reminiscent of ring canals and yolk plugs.

217 Septins were additionally shown to be essential for the structural and mechanical
218 integrity of human and mouse sperm. Septins localize specifically to the sperm
219 annulus, a cortical ring separating the midpiece and the principal piece of the tail
220 (Figure 2G) [45-48]. *Sept4* null male mice are sterile, have defective sperm
221 morphology with sharply bent or broken tails, impaired motility, and the annulus

222 structure missing [45,46]. Point mutations in SEPT12 have been found in infertile
223 human males leading to similar sperm phenotypes, which were also recapitulated in
224 Sept12 mutant mouse models [47,48].

225 A particularly revealing function of septins was discovered in the context of axon
226 myelination. Myelin septins and Anillin form filaments associated with the innermost
227 membrane layer of compact myelin, which organize longitudinally along myelinated
228 axons in the CNS (Figure 2H) [49]. Remarkably, Sept8 mutation in mice, in which
229 septins and Anillin are lost, causes myelin outfoldings and decelerated nerve
230 conduction. The septin-Anillin scaffold was proposed to stabilize compact myelin as
231 myelin membranes grow or new myelin segments intercalate between existing
232 sheaths.

233 A new contribution of septins to tissue integrity was discovered recently with the
234 requirement of septins for adult *Drosophila* wing morphogenesis [50]. Dorsal and
235 ventral wing surface adhesion during metamorphosis depends on laminin-associated
236 microtubule-actin-septin cables that are essential for resisting hydrostatic pressure
237 from the internal body cavity during head eversion (Figure 2I). Septin depletion leads
238 to the separation of wing surfaces, resulting in blistered wings, showing their role in
239 wing adhesion and preservation of organ shape. It is notable that microtubules and
240 actin fail to form compact cables in the absence of septins [50]. Interestingly, in laminin
241 mutant wings where actin and microtubules are uncoupled, Pnut localized to actin and
242 not to microtubules in the cables [50].

243 Finally, septin depletion leads to defective organogenesis. Sept7 knockout within the
244 mouse inner ear led to reduced sensory epithelial cells and excessive apoptosis,
245 leading to a hypoplastic inner ear Torii [51]. Sept7b depletion in zebrafish larvae
246 causes irregular heart morphology with disorganized and loosely packed myofibrils,
247 including faint and partly missing Z-discs, leading to cardiac dysfunction [52].
248 Interestingly, Sept7 localizes to the myotendinous junction which is the site of muscle
249 force transmission to tendons.

250

251 **Molecular mechanisms of septin function**

252 Isolation of native septins from *Drosophila* [53,54] and mammalian tissues [55,56] has
253 shown that septins form heteromeric complexes. Functional studies *in vivo* have
254 further provided solid evidence that septins form and function as heteromeric
255 complexes [7,12,21,23,25,37,40,43,48,49] and that septin complexes with distinct
256 septin composition can have distinct functions [10,20,40,57], and have additionally
257 suggested that some septins might perform functions independently of their presence
258 in complexes [43]. For organisms with both hexamers and octamers (Figure 1), their
259 relative functional relevance remains to be explored. Although native septins can
260 polymerize into filaments *in vitro* [53-55], septin filaments have never been visualized
261 in any animal model system in nondividing cells. What regulates septin polymerization
262 *in vivo* is altogether unknown. Recent super-resolution imaging of isolated cortices
263 from dividing sea urchin embryos visualized for the first time septin nanostructures at
264 the cytokinetic ring that suggest a septin filament-like network organization [58].

265

266 Figure 3 summarizes the network of interactions thought to control animal septin
267 localization and function. The septin-Anillin interaction is the only direct interaction that
268 has been consistently confirmed *in vivo* and shown to be crucial for septin recruitment
269 to the membrane/cortex in most cases. Rho-GTP binding to Anillin was recently shown
270 to be a prerequisite for septin binding in dividing cultured cells [59], but its relevance
271 *in vivo* remains to be tested. Importantly, in cultured cells, human and *Drosophila*
272 Anillin were reported to be nuclear during interphase, and localize to the cortex and
273 cleavage furrow only during division [60,61]. However, Anillin localization *in vivo* is
274 more complex, and can be cortical during interphase. The *C.elegans* Anillin has not
275 been detected in the nucleus [28]. Thus, whether cortical septin localization reflects
276 systematically the presence of Anillin (Figure 3) will be important to decipher. Whether
277 septins bind membranes, actin, myosin-II, or formins directly *in vivo* remains to be
278 shown.

279

280 **Conclusion and future directions**

281 The similarities in the phenotypes of septin-depleted tissues in very diverse biological
282 contexts might reflect that animal septins might perform much more similar functions
283 than previously thought, notably with respect to structural and mechanical integrity
284 both in dividing and nondividing tissues. A major challenge for future studies will be to
285 dissect the specific contribution of septins to cell and tissue mechanics, as well as to
286 establish the developmental signaling pathways that determine septin localization and
287 function *in vivo*.

288

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292

293 **Author contributions**

294 J.D. : Conceptualization, Investigation, Writing – original draft, Writing – review &
295 editing, Visualization; L.L., M.M : Conceptualization, Investigation, Writing – original
296 draft, Writing – review & editing, Visualization, Supervision, Project administration,
297 Funding acquisition

298

299 **Declaration of interest:** The authors declare no conflict of interest.

300

301 **Figure legends**

302

303 **Figure 1.** Septin complex composition for different animal model systems. Septins are
304 classified in four homology groups based on sequence similarity [62]. For a
305 classification of septins across kingdoms see [1]. Septin complexes are palindromes,
306 with each septin in two copies and in a specific position within the complex. Septins
307 can form tetramers, hexamers or octamers depending on the organism (right-most
308 column). Hexamers are composed of septins from the SEPT2, SEPT6, SEPT7 groups,
309 while octamers contain additional septins from the SEPT3 group. Septin names and
310 septin subunits in septin complexes use the same color code. Annotation of *Xenopus*

311 and zebrafish septins is based on the latest versions of Xenbase and ZFIN databases
312 (as of 20 January 2025) and [63].

313

314 **Figure 2.** Schematic overview of phenotypes in septin-depleted embryos and tissues.
315 See main text for details.

316

317 **Figure 3.** Simplified schematic overview of the network of interactions thought to
318 control animal septin localization and function, integrating *in vitro* and *in vivo* data from
319 all model systems. For the sake of simplicity, not all interactions are shown. For
320 example, Anillin interactions with Citron kinase [64,65] and the formin DIAPH3 [66,67]
321 are not included.

References

1. Shuman B, Momany M: **Septins From Protists to People**. *Front Cell Dev Biol* 2021, **9**:824850.
2. Mostowy S, Cossart P: **Septins: the fourth component of the cytoskeleton**. *Nat Rev Mol Cell Biol* 2012, **13**:183-194.
3. Dolat L, Hu Q, Spiliotis ET: **Septin functions in organ system physiology and pathology**. *Biol Chem* 2014, **395**:123-141.
4. Menon MB, Sawada A, Chaturvedi A, Mishra P, Schuster-Gossler K, Galla M, Schambach A, Gossler A, Forster R, Heuser M, et al.: **Genetic deletion of SEPT7 reveals a cell type-specific role of septins in microtubule destabilization for the completion of cytokinesis**. *PLoS Genet* 2014, **10**:e1004558.
5. Roseler S, Sandrock K, Bartsch I, Busse A, Omran H, Loges NT, Zieger B: **Lethal phenotype of mice carrying a Sept11 null mutation**. *Biol Chem* 2011, **392**:779-781.
6. Fuchtbauer A, Lassen LB, Jensen AB, Howard J, Quiroga Ade S, Warming S, Sorensen AB, Pedersen FS, Fuchtbauer EM: **Septin9 is involved in septin filament formation and cellular stability**. *Biol Chem* 2011, **392**:769-777.
7. Adam JC, Pringle JR, Peifer M: **Evidence for functional differentiation among Drosophila septins in cytokinesis and cellularization**. *Mol Biol Cell* 2000, **11**:3123-3135.
8. Cavini IA, Leonardo DA, Rosa HVD, Castro D, D'Muniz Pereira H, Valadares NF, Araujo APU, Garratt RC: **The Structural Biology of Septins and Their Filaments: An Update**. *Front Cell Dev Biol* 2021, **9**:765085.
9. Neufeld TP, Rubin GM: **The Drosophila peanut gene is required for cytokinesis and encodes a protein similar to yeast putative bud neck filament proteins**. *Cell* 1994, **77**:371-379.
10. O'Neill RS, Clark DV: **The Drosophila melanogaster septin gene Sep2 has a redundant function with the retrogene Sep5 in imaginal cell proliferation but is essential for oogenesis**. *Genome* 2013, **56**:753-758.
11. Morais-de-Sa E, Sunkel C: **Adherens junctions determine the apical position of the midbody during follicular epithelial cell division**. *EMBO Rep* 2013, **14**:696-703.
12. Fares H, Peifer M, Pringle JR: **Localization and possible functions of Drosophila septins**. *Mol Biol Cell* 1995, **6**:1843-1859.
13. Mavrakis M, Rikhy R, Lippincott-Schwartz J: **Plasma membrane polarity and compartmentalization are established before cellularization in the fly embryo**. *Dev Cell* 2009, **16**:93-104.
14. Afshar K, Stuart B, Wasserman SA: **Functional analysis of the Drosophila diaphanous FH protein in early embryonic development**. *Development* 2000, **127**:1887-1897.
15. Silverman-Gavrila RV, Hales KG, Wilde A: **Anillin-mediated targeting of peanut to pseudocleavage furrows is regulated by the GTPase Ran**. *Mol Biol Cell* 2008, **19**:3735-3744.
16. Sherlekar A, Rikhy R: **Syndapin promotes pseudocleavage furrow formation by actin organization in the syncytial Drosophila embryo**. *Mol Biol Cell* 2016, **27**:2064-2079.
17. Dey B, Mitra D, Das T, Sherlekar A, Balaji R, Rikhy R: **Adhesion and Polarity protein distribution-regulates hexagon dominated plasma membrane organization in Drosophila blastoderm embryos**. *Genetics* 2023, **225**.
18. Rikhy R, Mavrakis M, Lippincott-Schwartz J: **Dynamin regulates metaphase furrow formation and plasma membrane compartmentalization in the syncytial Drosophila embryo**. *Biol Open* 2015, **4**:301-311.
19. Xue Z, Sokac AM: **Back-to-back mechanisms drive actomyosin ring closure during Drosophila embryo cleavage**. *J Cell Biol* 2016, **215**:335-344.
20. Su J, Chow B, Boulianne GL, Wilde A: **The BAR domain of amphiphysin is required for cleavage furrow tip-tubule formation during cellularization in Drosophila embryos**. *Mol Biol Cell* 2013, **24**:1444-1453.
21. Mavrakis M, Azou-Gros Y, Tsai FC, Alvarado J, Bertin A, Iv F, Kress A, Brasselet S, Koenderink GH, Lecuit T: **Septins promote F-actin ring formation by crosslinking actin filaments into curved bundles**. *Nat Cell Biol* 2014, **16**:322-334.
22. Field CM, Coughlin M, Doberstein S, Marty T, Sullivan W: **Characterization of anillin mutants reveals essential roles in septin localization and plasma membrane integrity**. *Development* 2005, **132**:2849-2860.
23. Founounou N, Loyer N, Le Borgne R: **Septins Regulate the Contractility of the Actomyosin Ring to Enable Adherens Junction Remodeling during Cytokinesis of Epithelial Cells**. *Dev Cell* 2013, **24**:242-255.
24. Pinheiro D, Hannezo E, Herszterg S, Bosveld F, Gague I, Balakireva M, Wang Z, Cristo I, Rigaud SU, Markova O, et al.: **Transmission of cytokinesis forces via E-cadherin dilution and actomyosin flows**. *Nature* 2017, **545**:103-107.
25. Nguyen TQ, Sawa H, Okano H, White JG: **The C. elegans septin genes, unc-59 and unc-61, are required for normal postembryonic cytokineses and morphogenesis but have no essential function in embryogenesis**. *J Cell Sci* 2000, **113 Pt 21**:3825-3837.
26. Maddox AS, Lewellyn L, Desai A, Oegema K: **Anillin and the septins promote asymmetric ingression of the cytokinetic furrow**. *Dev Cell* 2007, **12**:827-835.
27. Jordan SN, Davies T, Zhuravlev Y, Dumont J, Shirasu-Hiza M, Canman JC: **Cortical PAR polarity proteins promote robust cytokinesis during asymmetric cell division**. *J Cell Biol* 2016, **212**:39-49.
28. Maddox AS, Habermann B, Desai A, Oegema K: **Distinct roles for two C. elegans anillins in the gonad and early embryo**. *Development* 2005, **132**:2837-2848.
29. Zaatri A, Perry JA, Maddox AS: **Septins and a formin have distinct functions in anaphase chiral cortical rotation in the Caenorhabditis elegans zygote**. *Mol Biol Cell* 2021, **32**:1283-1292.
30. Singh D, Odedra D, Dutta P, Pohl C: **Mechanical stress induces a scalable switch in cortical flow polarization during cytokinesis**. *J Cell Sci* 2019, **132**.
31. Finger FP, Kopish KR, White JG: **A role for septins in cellular and axonal migration in C. elegans**. *Dev Biol* 2003, **261**:220-234.
32. Kim SK, Shindo A, Park TJ, Oh EC, Ghosh S, Gray RS, Lewis RA, Johnson CA, Attie-Bittach T, Katsanis N, et al.: **Planar cell polarity acts through septins to control collective cell movement and ciliogenesis**. *Science* 2010, **329**:1337-1340.
33. Shindo A, Wallingford JB: **PCP and septins compartmentalize cortical actomyosin to direct collective cell movement**. *Science* 2014, **343**:649-652.
34. Park TJ, Kim SK, Wallingford JB: **The planar cell polarity effector protein Wdpcp (Fritz) controls epithelial cell cortex dynamics via septins and actomyosin**. *Biochem Biophys Res Commun* 2015, **456**:562-566.
35. Devitt CC, Weng S, Bejar-Padilla VD, Alvarado J, Wallingford JB: **PCP and Septins govern the polarized organization of the actin cytoskeleton during convergent extension**. *Curr Biol* 2024, **34**:615-622 e614.
36. Kho M, Hladyszau S, Tsygankov D, Nie S: **Coordinated regulation of Cdc42ep1, actin, and septin filaments during neural crest cell migration**. *Front Cell Dev Biol* 2023, **11**:1106595.

37. Gabbert AM, Campanale JP, Mondo JA, Mitchell NP, Myers A, Streichan SJ, Miolane N, Montell DJ: **Septins regulate border cell surface geometry, shape, and motility downstream of Rho in Drosophila**. *Dev Cell* 2023, **58**:1399-1413 e1395.
38. Zhai G, Gu Q, He J, Lou Q, Chen X, Jin X, Bi E, Yin Z: **Sept6 is required for ciliogenesis in Kupffer's vesicle, the pronephros, and the neural tube during early embryonic development**. *Mol Cell Biol* 2014, **34**:1310-1321.
39. Dash SN, Lehtonen E, Wasik AA, Schepis A, Paavola J, Panula P, Nelson WJ, Lehtonen S: **Sept7b is essential for pronephric function and development of left-right asymmetry in zebrafish embryogenesis**. *J Cell Sci* 2014, **127**:1476-1486.
40. O'Neill RS, Clark DV: **Partial Functional Diversification of Drosophila melanogaster Septin Genes Sep2 and Sep5**. *G3 (Bethesda)* 2016, **6**:1947-1957.
41. Hime GR, Brill JA, Fuller MT: **Assembly of ring canals in the male germ line from structural components of the contractile ring**. *J Cell Sci* 1996, **109 (Pt 12)**:2779-2788.
42. Price KL, Tharakan DM, Cooley L: **Evolutionarily conserved midbody remodeling precedes ring canal formation during gametogenesis**. *Dev Cell* 2023, **58**:474-488 e475.
43. Perry JA, Werner ME, Rivenbark L, Maddox AS: **Caenorhabditis elegans septins contribute to the development and structure of the oogenic germline**. *Cytoskeleton (Hoboken)* 2023, **80**:215-227.
44. Priti A, Ong HT, Toyama Y, Padmanabhan A, Dasgupta S, Krajnc M, Zaidel-Bar R: **Syncytial germline architecture is actively maintained by contraction of an internal actomyosin corset**. *Nat Commun* 2018, **9**:4694.
45. Ihara M, Kinoshita A, Yamada S, Tanaka H, Tanigaki A, Kitano A, Goto M, Okubo K, Nishiyama H, Ogawa O, et al.: **Cortical organization by the septin cytoskeleton is essential for structural and mechanical integrity of mammalian spermatozoa**. *Dev Cell* 2005, **8**:343-352.
46. Kissel H, Georgescu MM, Larisch S, Manova K, Hunnicutt GR, Steller H: **The Sept4 septin locus is required for sperm terminal differentiation in mice**. *Dev Cell* 2005, **8**:353-364.
47. Kuo YC, Lin YH, Chen HI, Wang YY, Chiou YW, Lin HH, Pan HA, Wu CM, Su SM, Hsu CC, et al.: **SEPT12 mutations cause male infertility with defective sperm annulus**. *Hum Mutat* 2012, **33**:710-719.
48. Kuo YC, Shen YR, Chen HI, Lin YH, Wang YY, Chen YR, Wang CY, Kuo PL: **SEPT12 orchestrates the formation of mammalian sperm annulus by organizing core octameric complexes with other SEPT proteins**. *J Cell Sci* 2015, **128**:923-934.
49. Patzig J, Erwig MS, Tenzer S, Kusch K, Dibaj P, Mobius W, Goebels S, Schaeren-Wiemers N, Nave KA, Werner HB: **Septin/anillin filaments scaffold central nervous system myelin to accelerate nerve conduction**. *Elife* 2016, **5**.
50. Sun T, Song Y, Teng D, Chen Y, Dai J, Ma M, Zhang W, Pastor-Pareja JC: **Atypical laminin spots and pull-generated microtubule-actin projections mediate Drosophila wing adhesion**. *Cell Rep* 2021, **36**:109667.
51. Torii H, Yoshida A, Katsuno T, Nakagawa T, Ito J, Omori K, Kinoshita M, Yamamoto N: **Septin7 regulates inner ear formation at an early developmental stage**. *Dev Biol* 2016, **419**:217-228.
52. Dash SN, Narumanchi S, Paavola J, Perttunen S, Wang H, Lakkisto P, Tikkanen I, Lehtonen S: **Sept7b is required for the subcellular organization of cardiomyocytes and cardiac function in zebrafish**. *Am J Physiol Heart Circ Physiol* 2017, **312**:H1085-H1095.
53. Field CM, al-Awar O, Rosenblatt J, Wong ML, Alberts B, Mitchison TJ: **A purified Drosophila septin complex forms filaments and exhibits GTPase activity**. *J Cell Biol* 1996, **133**:605-616.
54. Huijbregts RP, Svitin A, Stinnett MW, Renfrow MB, Chesnokov I: **Drosophila Orc6 facilitates GTPase activity and filament formation of the septin complex**. *Mol Biol Cell* 2009, **20**:270-281.
55. Kinoshita M, Field CM, Coughlin ML, Straight AF, Mitchison TJ: **Self- and actin-templated assembly of Mammalian septins**. *Dev Cell* 2002, **3**:791-802.
56. Hsu SC, Hazuka CD, Roth R, Foletti DL, Heuser J, Scheller RH: **Subunit composition, protein interactions, and structures of the mammalian brain sec6/8 complex and septin filaments**. *Neuron* 1998, **20**:1111-1122.
57. Stjepic V, Nakamura M, Hui J, Parkhurst SM: **Two Septin complexes mediate actin dynamics during cell wound repair**. *Cell Rep* 2024, **43**:114215.
58. Garno C, Irons ZH, Gamache CM, McKim Q, Reyes G, Wu X, Shuster CB, Henson JH: **Building the cytokinetic contractile ring in an early embryo: Initiation as clusters of myosin II, anillin and septin, and visualization of a septin filament network**. *PLoS One* 2021, **16**:e0252845.
59. Carim SC, Hickson GRX: **The Rho1 GTPase controls anillo-septin assembly to facilitate contractile ring closure during cytokinesis**. *iScience* 2023, **26**:106903.
60. Field CM, Alberts BM: **Anillin, a contractile ring protein that cycles from the nucleus to the cell cortex**. *J Cell Biol* 1995, **131**:165-178.
61. Oegema K, Savoian MS, Mitchison TJ, Field CM: **Functional analysis of a human homologue of the Drosophila actin binding protein anillin suggests a role in cytokinesis**. *J Cell Biol* 2000, **150**:539-552.
62. Kinoshita M: **Assembly of mammalian septins**. *J Biochem* 2003, **134**:491-496.
63. Van Ngo H, Robertin S, Brokatzky D, Bielecka MK, Lobato-Marquez D, Torraca V, Mostowy S: **Septins promote caspase activity and coordinate mitochondrial apoptosis**. *Cytoskeleton (Hoboken)* 2023, **80**:254-265.
64. El-Amine N, Carim SC, Wernike D, Hickson GRX: **Rho-dependent control of the Citron kinase, Sticky, drives midbody ring maturation**. *Mol Biol Cell* 2019, **30**:2185-2204.
65. Gai M, Camera P, Dema A, Bianchi F, Berto G, Scarpa E, Germena G, Di Cunto F: **Citron kinase controls abscission through RhoA and anillin**. *Mol Biol Cell* 2011, **22**:3768-3778.
66. Watanabe S, Okawa K, Miki T, Sakamoto S, Morinaga T, Segawa K, Arakawa T, Kinoshita M, Ishizaki T, Narumiya S: **Rho and anillin-dependent control of mDia2 localization and function in cytokinesis**. *Mol Biol Cell* 2010, **21**:3193-3204.
67. Chen A, Arora PD, McCulloch CA, Wilde A: **Cytokinesis requires localized beta-actin filament production by an actin isoform specific nucleator**. *Nat Commun* 2017, **8**:1530.

*** of special interest**

29. Zaatri A, Perry JA, Maddox AS: **Septins and a formin have distinct functions in anaphase chiral cortical rotation in the Caenorhabditis elegans zygote**. *Mol Biol Cell* 2021, **32**:1283-1292.

This study reports that septins are required for chiral rotation of the cortex in the *C.elegans* zygote. Whereas the formin CYK-1 controls the chirality of rotation, septins translate cytoskeletal chirality to whole-cell cortical rotation by controlling formin polarization and possibly cross-linking different actin bundle populations.

57. Stjepic V, Nakamura M, Hui J, Parkhurst SM: **Two Septin complexes mediate actin dynamics during cell wound repair.** *Cell Rep* 2024, **43**:114215.

This study uses laser injury of *Drosophila* syncytial blastoderm embryos as a model system for cell wound repair. Although all five *Drosophila* septins are required for efficient wound repair, this study reports the presence of two functionally distinct septin complexes, Sep1/Sep2/Pnut and Sep4/Sep5/Pnut, only the former of which is regulated by Anillin.

58. Garo C, Irons ZH, Gamache CM, McKim Q, Reyes G, Wu X, Shuster CB, Henson JH: **Building the cytokinetic contractile ring in an early embryo: Initiation as clusters of myosin II, anillin and septin, and visualization of a septin filament network.** *PLoS One* 2021, **16**:e0252845.

This study uses super-resolution imaging to report the first nanostructural organization of septins and Anillin in dividing animal embryos. Using isolated cortices of sea urchin embryos, this study supports the organization of septins in a filament-like meshwork in the assembling cytokinetic ring, with septins being centrally localized with respect to myosin-II minifilament head groups.

**** of outstanding interest**

37. Gabbert AM, Campanale JP, Mondo JA, Mitchell NP, Myers A, Streichan SJ, Miolane N, Montell DJ: **Septins regulate border cell surface geometry, shape, and motility downstream of Rho in *Drosophila*.** *Dev Cell* 2023, **58**:1399-1413 e1395.

This study shows that septins are required for proper delamination and migration of border cell clusters in the *Drosophila* egg chamber. Importantly, although septins and myosin-II colocalize dynamically during this process, Rho independently regulates myosin activity and septin localization.

43. Perry JA, Werner ME, Rivenbark L, Maddox AS: **Caenorhabditis elegans septins contribute to the development and structure of the oogenic germline.** *Cytoskeleton (Hoboken)* 2023, **80**:215-227.

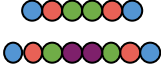


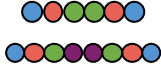
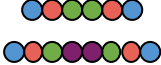
This study reports that the two *C.elegans* septins UNC-59 and UNC-61 act together to control the development and architecture of the oogenic germline, but also provide evidence that each septin has distinct functions. Importantly, septin depletion leads to irregular and vesiculated germ cell compartment and oocyte plasma membranes pointing to important roles in membrane integrity.

50. Sun T, Song Y, Teng D, Chen Y, Dai J, Ma M, Zhang W, Pastor-Pareja JC: **Atypical laminin spots and pull-generated microtubule-actin projections mediate *Drosophila* wing adhesion.** *Cell Rep* 2021, **36**:109667.

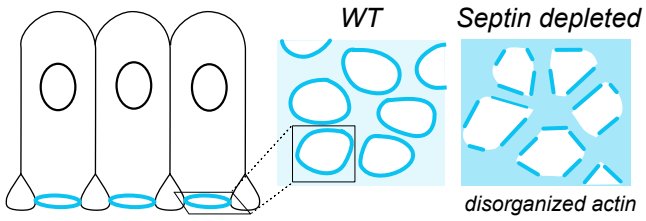
This study shows that septins are required for wing morphogenesis during *Drosophila* metamorphosis. Septins are needed to compact actin and microtubules into dorsoventral cables essential for resistance to hydrostatic pressure from the internal body cavity during head eversion.

59. Carim SC, Hickson GRX: **The Rho1 GTPase controls anillin-septin assembly to facilitate contractile ring closure during cytokinesis.** *iScience* 2023, **26**:106903.

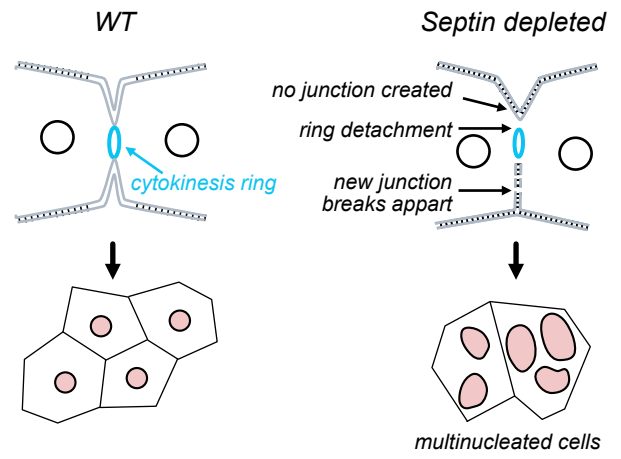
This study uses *Drosophila* S2 cells and HeLa cells to show that Anillin-mediated septin recruitment to the cytokinetic ring requires not only the C-terminal PH domain of Anillin, but also binding to Rho1-GTP.

	SEPT2 Group	SEPT6 Group	SEPT7 Group	SEPT3 Group	Septin complexes
Mouse	Sept1 Sept2 Sept4 Sept5	Sept6 Sept8 Sept10 Sept11 Sept14	Sept7	Sept3 Sept9 Sept12	
Drosophila	Sep1 Sep4	Sep2 Sep5	Pnut		
C. elegans		UNC-61	UNC-59		
Zebrafish	Sept2 Sept4a Sept4b Sept5a Sept5b zgc:63587 zgc:162239	Sept6 Sept8a Sept8b Sept10	Sept7a Sept7b Sept15	Sept3 Sept9a Sept9b Sept12	
Xenopus	Sept2 Sept4 Sept5	Sept6 Sept8 Sept10 Sept11	Sept7	Sept3 Sept9 Sept12	

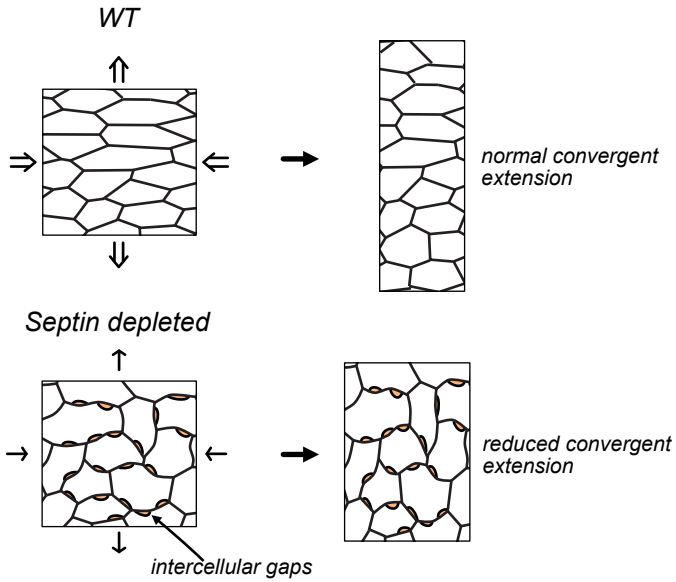
A Drosophila cellularisation



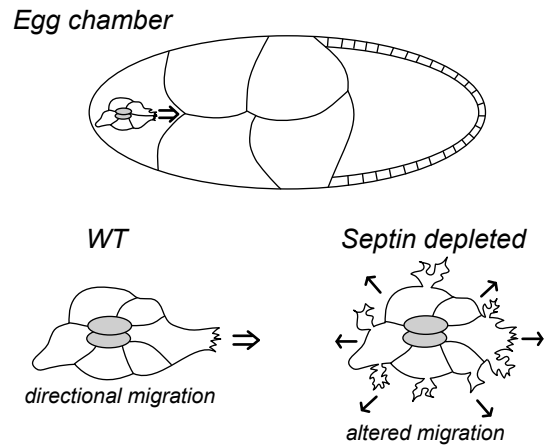
B Drosophila epithelial cell division



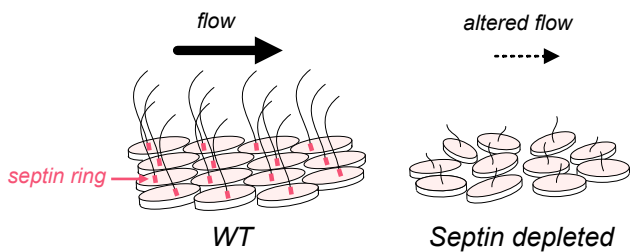
C Xenopus convergent extension



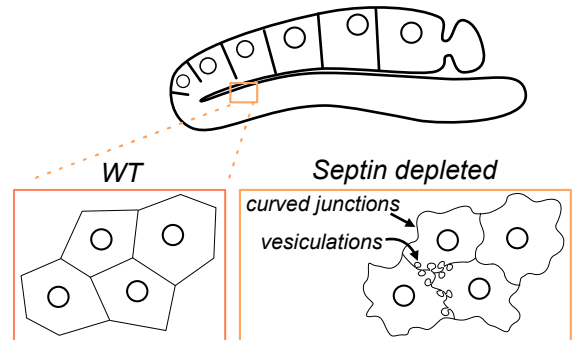
D Drosophila border cell migration



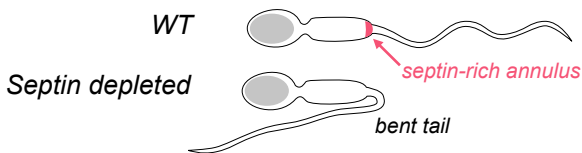
E Cilium formation - left/right asymmetry



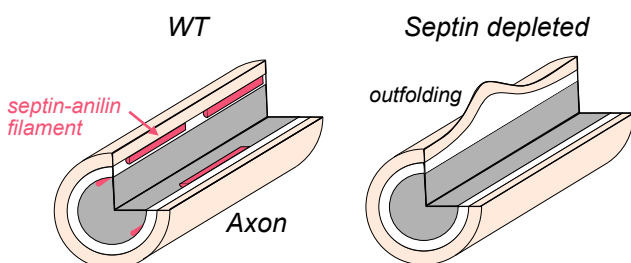
F C. elegans germline architecture



G Mouse sperm morphogenesis



H Compact myelin formation



I Drosophila wing basal cell adhesion

