**Title**
Cell-autonomous immunity and the endosymbiotic theory: Septins at the origin?

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**Highlights**
- Early eukaryotes evolved to distinguish prey, pathogens, and potential endosymbionts
- Septins are curvature-sensing GTP-binding proteins already present in the LECA
- Septins bind bacteria and bacteria-derived organelles across eukaryotes
- Septin immunity and organelle control may share one ancestral function
- Septins may have been co-opted recently to associate with plasma/endomembrane

**Abstract**
The origin of complex eukaryotic cells remains a long-standing mystery. Endosymbiosis gave rise to mitochondria and chloroplasts, the bacteria-derived organelles that underpin eukaryotic productivity. Early eukaryotes had to establish these partnerships while avoiding pathogens, using limited ancestral tools. Septins are cytoskeletal GTP-binding proteins best known for roles in cytokinesis, yet their core function remains unclear. Their presence in algae and ciliates places septins in the last eukaryotic common ancestor (LECA). We propose that the ancestral septin recognised foreign cells, and that this single function later diversified into chloroplast and mitochondrial fission and into innate immunity against pathogens. Here we examine the mechanisms and consequences of bacterial recognition by septins, and outline the organisms and approaches needed to test this model.

**Main text**

**Introduction: Ancestral immunity at the origin of eukaryotes**
Eukaryotes are the product of a 2-billion-year-old merger. Comparative genomics places the host within the Asgard archaea and the mitochondrial ancestor within or beside the alphaproteobacteria (1, 2). What those reconstructions do not tell us is how the host survived the encounter. Every proposed route to the mitochondrion - external syntrophy, phagocytosis, or the domestication of a bacterial pathogen - requires the host cell to have held a live bacterium in prolonged contact without digesting it or being killed by it (3-5). The outcome is the same in each case: the same host cell might hold prey, a pathogen, or a future organelle, and the three had to be told apart. This is arguably a eukaryote-specific imperative arising from the evolutionary transition to a heterotrophic lifestyle capable of phagocytosis (**Figure 1AB**).

How early eukaryotes did so is essentially unknown. Bacteria carry dozens of anti-phage systems; plants discriminate self from non-self through NLR receptors and an expanded AIG1 family; animals combine pattern recognition with a cell-autonomous arm that acts on

pathogens already in the cytosol (6, 7). For the eukaryotic stem lineage there is no comparable inventory. Reconstructions return an already-complex last common ancestor whose defense repertoire remains largely unannotated (1, 8).

Septins are an informative place to look, for a reason unconnected to their familiar roles. They belong to the TRAFAC class of P-loop GTPases, within the TrmE–Era–EngA–EngB–septin superfamily (9). Their closest eukaryotic relatives, the paraseptins, are consistent with a defence-related ancestry (10). GIMAP2 was crystallised as a septin-like GTPase (11), and a search seeded on bacterial anti-phage systems identified human GIMAP5 and GIMAP6 as antiviral descendants of the anti-phage Eleos system (12). Septins were recovered by the same search but set aside because they were classified as having no documented immune role. Phylogeny now places the chloroplast import receptors TOC34 and TOC159 within the septin radiation (13), whereas the position of AIG1/GIMAP has not been tested, leaving the question of an ancestral defense function open. This article asks whether the recognition of bacteria, chloroplasts and mitochondria by extant septins is the residue of that ancestral function (**Figure 1**).

**History of septin-bacteria interactions**

Septins were first described as cell-division-cycle genes required for cytokinesis in budding yeast, where they assemble into a filamentous collar and rings at the mother-bud neck (14). Since then, septins have mostly been studied as scaffolds for cytokinesis, cell polarity, and membrane compartmentalization in yeast and animal cells. Their relevance to infection biology went unappreciated until reports in the 2000s first described septin recruitment to invasive bacterial pathogens (15).

In 2010 work showed that human septins assemble into cage-like structures that entrap cytosolic *Shigella flexneri* (Figure 2A), an important human pathogen and cellular microbiology paradigm historically used for innate immune discovery, restricting their actin-based motility and cell-to-cell dissemination (16). This discovery reframed septins as structural determinants of host defense and as bona fide components of cell-autonomous immunity (7). Septin cages were subsequently shown to cooperate with ubiquitin-mediated selective autophagy: entrapped bacteria were decorated with ubiquitin and recognized by autophagy receptors, integrating septin-cage entrapment with lysosomal degradation (16-18).

How do septins recognize bacteria for cage entrapment? Work performed in tissue culture cells (19) and in vitro using purified proteins (20) showed that septins recognize micron-scale membrane curvatures, biophysical properties of bacterial poles and division septa. Because dividing bacterial cells present curved surfaces that are biophysically and/or biochemically distinct from host membrane, septins act as curvature sensors that preferentially entrap cytosolic, metabolically active (i.e., dividing) bacteria, linking bacterial cell biology to recognition by cell-autonomous immunity. Reconstitution studies with purified septins confirmed that curvature sensing can promote cage assembly in vitro, highlighting a biophysical basis for pathogen recognition that does not rely on conventional pattern-recognition mechanisms (20, 21).

High-content imaging and deep-learning-assisted analyses revealed heterogeneity in septin caging across individual bacteria and host cells, suggesting that septin-mediated immunity is a probabilistic strategy of host defense (rather than a binary all-or-nothing recognition of bacterial cells) (22). Septin-mediated immunity has since extended beyond *Shigella* to other cytosol-dwelling and vacuolar pathogens, as well as viruses (23), and has connected septins to additional arms of host defense, including inflammasome regulation and gasdermin D-dependent pyroptosis (24, 25). In agreement with our proposal that bacterial recognition is an ancestral septin trait, pathogens evolved countermeasures: *Shigella* effectors shield bacterial surfaces from septin and autophagy recognition (16, 20), and more recent work identified

promotion of septin ubiquitination and ADP-riboxanation to prevent cage formation (26-28), illustrating an ongoing evolutionary arms race at the cytoskeleton-pathogen interface.

**From bacterial recognition to chloroplast regulation**

Septin recruitment to intracellular bacteria in animal cells has generally been viewed as evidence that septins acquired a specialized function for cell-autonomous immunity (7, 15). The recent discovery that algal septins associate with chloroplasts (13), however, offers a fundamentally different evolutionary perspective. Rather than representing an isolated immune function, bacterial recognition may reflect an ancestral property of the septin family that predates the diversification of modern eukaryotes. Fundamentally, chloroplasts are domesticated cyanobacteria that have co-evolved with their hosts for likely over a billion years. If septins had an ancestral role in recognizing bacteria and bacteria-derived compartments, chloroplasts, with their outer membrane derived from the ancestral cyanobacterial endosymbiont, offer an opportunity to examine how this recognition evolved from host defense to host-imposed control.

The unicellular green alga *Chlamydomonas reinhardtii* is particularly informative in this regard. Whereas fungi and animals possess multiple septin paralogs that assemble into hetero-oligomeric complexes, *Chlamydomonas* retains a single septin, SEP1, likely resembling a simpler state that existed early during eukaryotic evolution (29-34). In vitro, SEP1 homo-dimerizes through its central GTP interface (32, 35). In vivo, rather than localizing to the plasma membrane or cleavage furrow, SEP1 forms filamentous assemblies on the chloroplast envelope during interphase and reorganizes into a ring at the chloroplast division site during mitosis (**Figure 2B**) (13). Loss of SEP1 selectively disrupts the import and positioning of chloroplast division proteins while leaving bulk chloroplast protein import largely unaffected, indicating that septin specifically coordinates the machinery required for organelle division. Most unexpectedly, SEP1 physically associates with the TOC GTPases that initiate chloroplast protein import, and molecular phylogeny suggests that these TOC receptors themselves originated from an ancestral algal septin lineage (13).

These observations invite a reinterpretation of septin biology through an evolutionary rather than a cell biological lens. Rather than viewing chloroplast localization as a newly acquired septin function, it may represent the retention of an ancestral interaction with bacterial-derived membranes. The significance of the observation is therefore not that septins associate with chloroplasts, but that this association has been maintained while its biological outcome has changed. A recognition system that may once have organized intracellular bacteria now coordinates protein import, division, and inheritance of a permanently domesticated endosymbiont.

Permanent integration of the cyanobacterial endosymbiont required the evolution of a protein import apparatus capable of returning thousands of nucleus-encoded proteins to the organelle following endosymbiotic gene transfer (36, 37). Among the components of the large translocon complex are the two outer-envelope preprotein receptors, TOC34 and TOC159, which are GTPases (38, 39). It has been proposed that an unknown ancestral GTPase of eukaryotic origin evolved into TOCs in plants and GIMAP/IAN-family immune proteins in animals and plants (40). Based on the physical and functional interactions and phylogeny (10, 13), we propose that TOC GTPases evolved through modification of an existing septin lineage. In this view, the TOC GTPases are not simply distant relatives of septins but a highly specialized septin lineage, in which the ancestral filament-forming property was lost while the membrane-associated GTPase module was retained.

This hypothesis also provides a parsimonious explanation for one of the central challenges of primary endosymbiosis. The earliest photosynthetic eukaryotes did not necessarily need to evolve an entirely new system to manage an intracellular cyanobacterium. Instead, they may have adapted an existing bacterial-recognition module, progressively redirecting it toward

regulating protein import, organelle division, and ultimately host control of the endosymbiont (40). Such a scenario would explain why septins remain associated with processes that define chloroplast identity despite the enormous evolutionary distance separating modern chloroplasts from their cyanobacterial ancestors.

If chloroplasts illustrate how septins were adapted to control a domesticated cyanobacterium, an obvious question follows. Did a similar evolutionary trajectory accompany another endosymbiotic event that defined the origin of eukaryotes? The widespread association of septins with mitochondria suggests that this ancestral relationship between septins and bacterial-derived compartments may extend across both organelles that fundamentally shaped the eukaryotic cell.

**Mitochondria and their interactions with septins**

Like chloroplasts, mitochondria are descended from eubacteria through a process of endosymbiosis (41, 42). The precise bacterial precursor of mitochondria is thought to be either an alphaproteobacteria (43-45) or a member of a sister group (46-48).

As with chloroplasts, how mitochondria came to be inside the archaeal ancestor of the eukaryotic cell is still not fully resolved. Possible scenarios include an initially external symbiosis that gradually involved one cell surrounding the other entirely (3), active phagocytosis of the bacteria by a phagocytosis-capable cell (49, 50), or intrusion of the bacteria into the cytoplasm of the host cell as a pathogen or foreign inclusion (5). The phagocytosis-first model for mitochondria is particularly problematic compared to the case of chloroplasts, given that the energetics of phagocytosis, particularly acidification of the food vacuole, require the mitochondrion to already be present (4). This would not have been an issue for chloroplasts, which are thought to have arisen in host cells that already contained mitochondria. Also inconsistent with the phagocytosis-first model is the extensive evidence that the outer mitochondrial membrane retains components of the bacterial outer membrane, such as β-barrel proteins (42, 51) and cardiolipin (52). Thus, if septin-bacterium recognition formed part of an ancestral cell-autonomous immune system, septins may have been predisposed to associate with the bacterial-derived surface of the proto-mitochondrion. Given the interest in the mechanism of how mitochondrial precursors entered the host cell, the multifarious roles of septins in interacting with foreign bacteria may hold part of the answer, and it is to be hoped that future studies will shed light on this connection. In the meantime, we can look for clues in the current roles that septins play in mitochondrial biology, particularly with regard to regulating growth and division of mitochondrial networks.

In many species, mitochondria form elaborate connected networks (53), whose branched structure can vary as a function of metabolic or disease states (54). This network is thought to play a role either in distribution of metabolic products including ATP (55) or in inheritance of the mitochondrial genomes (56, 57). Network-like mitochondria are seen throughout the eukaryotes including not only yeast and mammalian cells, but also green algae such as *Chlamydomonas* (58), apicomplexans (59), trypanosomes (59), and euglenozoa (60). In contrast, in ciliates like *Tetrahymena* and *Stentor*, mitochondria form small, individual bacteria-sized spheroids closely associated with the cell cortex (61, 62). A similar unbranched, spheroidal morphology is seen in *Dictyostelium* (63), and in many green plants including *Arabidopsis* (64, 65).

The network architecture of mitochondria depends on a combination of fission and fusion (66, 67). Fission and fusion even occur in species in which the mitochondria are present as separated spherules rather than as networks (63). In most cases, fission and fusion are carried out by means of host-encoded proteins, with the major driver of fission being the dynamin-related GTPase Drp1, also known as Dlp1 and Dnm1 depending on the species (68-70), although some protists and algae use FtsZ of bacterial origin, exclusively or together with dynamin (71).

In many organisms, although apparently not budding yeast, mitochondrial fission involves septins. This was first discovered in the ciliate *Tetrahymena*, in which it was found that septins, co-localize with mitochondria and control fission (**Figure 2C**). In mammalian cells, Septin 2 (Sept2) interacts directly with Drp1 and localizes to mitochondrial constrictions(**Figure 2D**). Knockdown of Sept2 led to hyper-fused mitochondria and a reduction in mitochondrial fission rates, due at least in part to reduced recruitment of Drp1 (72, 73). The effect was specific to fission; fusion rates were unaffected by Sept2 knockdown. Similar effects of septins on mitochondrial fission were seen in macrophages (74), mouse muscle cells (75), and in *Caenorhabditis elegans* (72).

Cryo-EM of mitochondrial constrictions in mammalian cells revealed septin filaments closely associated with the OMM in the restrictions (76) that tracked the local curvature of the OMM, consistent with a possible role in curvature sensing typical of septin function in other contexts. This leads to the hypothesis that septins may identify and/or create regions of high curvature and then recruit Drp1 to those regions. On the other hand, some septin isoforms may have a function in fission that occurs prior to Drp1 recruitment involving a Rho exchange factor (77).

**Discussion: What is the ancestral function of septins?**

Septins have traditionally been viewed through the lens of fungi and animals, where they function as membrane-associated cytoskeletal polymers that regulate cytokinesis, cell polarity, membrane trafficking, ciliary function, and numerous other cellular processes (78, 79). This remarkable functional diversity has made it difficult to identify a unifying principle underlying septin biology. We suggest that this difficulty arises because the functions most intensively studied today are unlikely to represent the earliest functions acquired during evolution.

Here, based on the key points summarized in **Box 1**, we propose an “immunity-first” hypothesis for septin evolution:

- Early eukaryotes had to establish endosymbiosis while avoiding harmful pathogens using limited ancestral tools available.
- An ancestral septin was an ancient eukaryotic immune protein against foreign bacterial cells; it worked by sensing curvature and/or bacterial membrane molecular features and then forming a polymeric cage around the bacterium.
- Septins evolved into positive/negative regulators of chloroplast division, mitochondrial fission, and bacterial replication.
- Expansion of septin roles into regulators of other processes, such as cytokinesis and membrane trafficking, happened in some lineages and was associated with septin duplications and loss of bacterial recognition in some paralogs.

Alternatives to this model would include a “cytokinesis-first” hypothesis, in which septins played a role in cytokinesis in LECA and were subsequently lost in all eukaryotic lineages except opisthokonts; they would independently acquire new traits to bind to bacteria and bacteria-derived organelles. A “membrane-association-first” hypothesis, in which the micron-scale curvature preference and anionic-lipid affinity are the ancestral traits and interactions with bacteria, organelles, and endomenbranes are all independent evolution. We favor the immunity-first model, even though it is admittedly speculative, as it follows the rule of parsimony based on the key points **(Box 1)** and thus “makes sense in the light of evolution” (adapted from (80)). The speculative nature stems from the dearth of information on septin biology outside well-studied fungi and animals (34). The model also raises new questions in septin biology from evolutionary perspectives.

**Outstanding Questions**

**What was the ancestral septin function?** Membrane sensing has the broadest published support: polybasic regions in all groups but one, amphipathic helices in all groups. Cytokinesis is limited outside opisthokonts. Immunity is the model proposed here, and remains untested

outside animals. Would a reconstructed ancestral septin discriminate live bacteria from curvature-matched inert templates?

**Did septins and their paraseptin relatives share a defence-related ancestor?** A single tree combining bacterial anti-phage GTPases, GIMAP and plant AIG1, septins, and TOC34/159 would place any ancestral defence function either at the septin node or one node deeper. Are GIMAPs nested within septins, septins within GIMAPs, or do both radiate from a defence protein?

**How and why did the transition from "recognizing foreign cells" to "binding to the eukaryotic endomembranes" occur in the animal/fungal lineage?**

An early transition in the opisthokont lineage may have altered septin substrate specificity from bacteria-derived membranes to the inner leaflet of the plasma membrane and the endomembrane system. Such a shift would have allowed septins to gain new functions in numerous membrane-associated processes that characterize fungi and animals. How do septins discriminate among multiple binding targets within a single cell? Are there complexes of different subunit compositions dedicated to individual targets? Can one complex be regulated to bind to different targets?

**Why did septins expand independently in some lineages?**

Septin genes have expanded independently in all three major eukaryotic branches in which they are found (34). These expansion events undoubtedly reflect diversification of septin-binding targets and/or functions. Whether these paralogs assemble into functional heterooligomeric complexes, in contrast, warrants careful consideration. It is formally possible that these paralogs form separate homopolymers that bind to distinct targets.

**Why have septins been lost so often?** Land plants, excavates and apicomplexans lack them, yet organelle division proceeds. Have other proteins taken over, or have septins diverged past recognition on long branches? Profile-based searches keep recovering septins that similarity searches miss.

**What would falsify an immunity-first origin?** Ancestral septins that bind chloroplast and mitochondrial membranes but show no preference for live bacteria over inert templates of matched geometry would favour a curvature-first origin instead.

## Concluding Remarks

Cell-autonomous immunity may represent one evolutionary outcome of an ancestral recognition system rather than its origin. Early eukaryotes almost certainly faced the challenge of defending themselves against intracellular pathogens while establishing stable relationships with endosymbionts. A membrane-organizing system that can recognize bacteria-derived compartments would have been ideally positioned to participate in both processes. Following endosymbiosis, this same machinery could have been retained and co-opted to regulate chloroplasts and mitochondria as they were domesticated to become host-regulated organelles. From this perspective, bacterial defense and organelle regulation are not independent septin functions but two consequences of the same ancestral molecular function.

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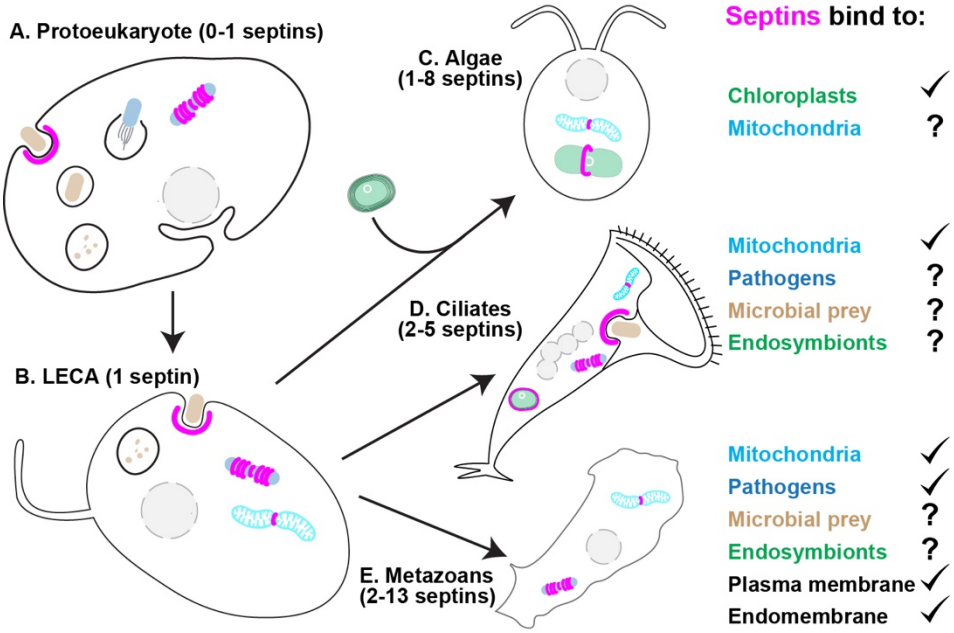


**Figure 1. Summary of our evolutionary hypotheses.**
(A) Protoeukaryotes had an ancestral septin that was involved in recognition and regulation of bacteria engulfed as prey or pathogens. (B) The ancestral septin was coopted to promote fission of alphaproteobacteria, leading to the establishment of mitochondria. (C) In algae, septin function is further coopted to regulate fission of chloroplasts, an organelle of cyanobacterial origin. (D) In ciliates, septins are known to regulate mitochondrial fission. (E) Metazoan septins regulate both mitochondria and bacterial pathogens. While not tested, they may also be involved in recognizing microbial prey and endosymbionts in invertebrates (81, 82). Numbers of (inferred) septin genes are based on (34).

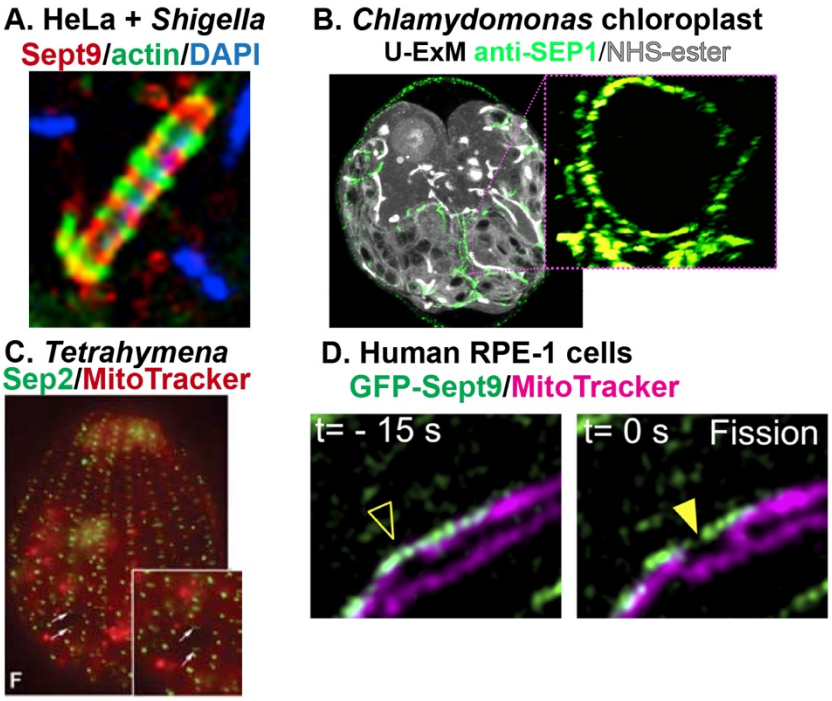


**Figure 2. Representative microscopy images of septins on bacteria and bacteria-derived organelles.**
(A) Septin forms a cage around invading bacteria in HeLa cells (16). (B) Septin forms a ring at the chloroplast division site in *Chlamydomonas* (13). (C) Septin colocalizes with mitochondria in the ciliate *Tetrahymena* (83). (D) Septin associates with the mitochondria fission site in RPE-1 cells (77).

**Box 1. Our new evolutionary perspective.**

- Early eukaryotic evolution involved a series of endosymbiotic events between eukaryotic cells and bacteria, during which the host needed to distinguish among prey, pathogens, and potential endosymbionts. This is a eukaryote-specific challenge as they became heterotrophs through the invention of phagocytosis. It likely involved an ancestral recognition system for foreign cells, reminiscent of the cell-autonomous immunity in modern animals, which recognizes foreign cells and activates the downstream cellular defense response.
- Much remains to be discovered about how the cell-autonomous immune system works, even in the most well-studied animal systems, but septins appear to be key a regulator.
- Septins bind to organelles of endosymbiotic origin in animals (mitochondria), ciliates (mitochondria), and algae (chloroplasts), covering all three major eukaryotic supergroups in which septins are found to date. In contrast, involvement of septins in association with the plasma membrane has been reported “only” (although there are many) in animals and fungi.
- Septins share sequence homology with other GTPases involved in immune response in both prokaryotes and eukaryotes.

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