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Review

Multinucleation as a recurring evolutionary strategy for scaling and plasticity

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SUMMARY

Multinucleate cells — single cells containing multiple nuclei in a shared cytoplasm — are found across the eukaryotic tree of life. Having evolved independently in fungi, plants, protists, and animals, they thrive in environments ranging from nutrient-poor deep-sea sediments to dynamic soil microhabitats and host tissues. Multinucleate organization enables spatial specialization without internal partitions and facilitates rapid scaling of metabolic or transcriptional capacity, allowing organisms to forage across patchy resources, withstand physical stress, and respond quickly to environmental fluctuations. Yet multinucleation also brings challenges, including diffusion limits, the need for nuclear coordination, and the potential for genetic conflict. Its repeated emergence, often in lineages that have also evolved multicellularity, points to shared cellular, structural, and regulatory prerequisites shaped by ecological pressures. Here, we integrate perspectives from cell biology, ecology, and evolution to demonstrate that multinucleation is not a rare anomaly but a fundamental organizational strategy. Recognizing these systems as adaptive responses to environmental constraints provides a framework for uncovering general principles of cellular organization, evolution of life-cycle strategies, and the diversification of complex life.

Introduction

Multinucleate cells, those containing multiple nuclei within a shared cytoplasm, are a widespread feature of eukaryotic life. These cells occur across diverse lineages and groups, including fungi[1,2], protists[3–6], plants and algae[7–11], and animals[12–14] (Figure 1, and Table S1 in Supplemental information). Their repeated emergence across the tree of life points to strong selection for cellular architectures that achieve large-scale integration without constructing and maintaining intercellular boundaries. The ecological and functional diversity of multinucleate cells, from terrestrial to marine, parasitic to free-living (Box 1), underscores their remarkable adaptive capacity.

Two fundamentally distinct routes give rise to multinucleate cells: nuclear division can proceed without cytokinesis, forming coenocytes (Figure 2A), or initially separate cells can fuse to form syncytia (Figure 2B). Despite their mechanistic differences, both routes converge on the same organizational outcome: multiple nuclei residing in a continuous cytoplasm, enabling spatial specialization without physical partitions, as well as rapid scaling of biosynthetic capacity and the redistribution of resources across large intracellular distances. These properties are based on conserved features such as cytoskeletal organization, nuclear positioning, and post-transcriptional regulation that recur across independent lineages[15–21]. Multinucleation can also arise in pathological contexts, where both failed mitotic exit and cell–cell fusion can result from genotoxic stress or viral infection, producing multinucleated cells that are associated with genomic instability or tissue dysfunction, including polyploid giant cancer cells[22] or virus-induced syncytia[23,24] (Figure 2C). Regardless of how these cells form, however, having multiple genomes within a shared cytoplasm expands the potential for genomic output and intracellular scaling, although the consequences of multinucleation depend strongly on how it is controlled.

Multinucleation is not the only solution to the challenge of expanding biosynthetic capacity beyond the limits of uninucleate, haploid organization. Polyploidy is an alternative solution. While multinucleation distributes genomes among multiple nuclei within a shared cytoplasm, polyploidy concentrates extra genome copies within a single nucleus[25–27]. Interestingly, these strategies are not mutually exclusive, as polyploid nuclei can be found in multinucleate cells[28,29]. Despite their shared capacity for genomic amplification, multinucleation and polyploidy differ in organization and control. Polyploidy centralizes regulation within one enlarged nucleus, favoring coordination but limiting spatial specialization, whereas multinucleation enables local transcriptional activity and responsiveness to spatial cues[26,30–33].

Both simple and complex multicellularity address similar scaling problems through yet another organizational solution. By partitioning nuclei into discrete cells, division of labor and compartmentalized regulation can be achieved, but at the cost of the construction and maintenance of intercellular boundaries and communication systems. Although multinucleation and multicellularity are often discussed as distinct organizational strategies, in reality they lie along a continuum of cytoplasmic connectivity. Many multicellular systems retain partial cytoplasmic continuity through incomplete abscission or stable intercellular bridges that permit the exchange of signals, organelles,

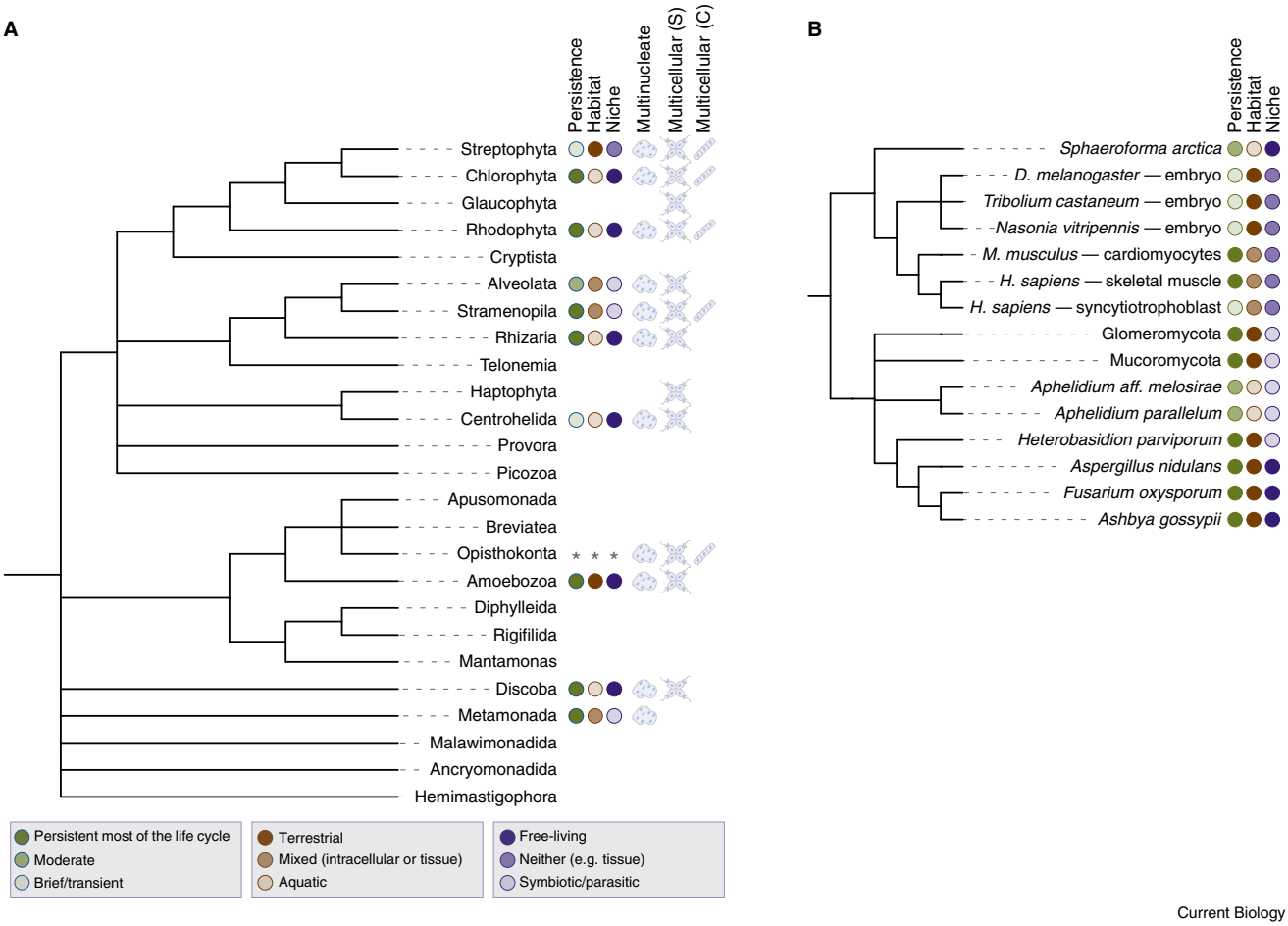

Figure 1. Ecological and organizational distribution of multinucleation across the eukaryotic tree of life.
(A) A collapsed eukaryotic tree of life illustrating the phylogenetic breadth of multinucleate and multicellular architectures across major eukaryotic clades. For each lineage, three ecological attributes are annotated using color-coded circles: persistence of the multinucleate state relative to the life cycle of the organism (green), habitat (brown), and niche (blue). Opisthokonta are highlighted with asterisks and expanded in (B). Icons to the right indicate whether the lineage contains multinucleate cells, simple multicellularity (S), and/or complex multicellularity (C). The figure highlights the repeated and phylogenetically widespread emergence of multinucleation across eukaryotes, as well as its co-occurrence with the other cellular architectures. The tree was visualized and annotated using the Interactive Tree Of Life (iTOL) v6[149]. (B) Expanded view of Opisthokonta, showing finer-scale annotation of fungi, animals, and closely related lineages. The taxa shown represent a non-exhaustive sampling of multinucleate architectures within this clade, including fungal coenocytic hyphae and animal syncytia. Persistence is defined relative to the life cycle of the organism rather than the duration of a specific cell type (e.g. human skeletal muscle is scored as persistent because multinucleation persists throughout the organism's lifetime, whereas placental syncytiotrophoblasts are transient relative to the human lifespan). In insects, multinucleation occurs during specific developmental stages, such as the coenocytic blastoderm of the *Drosophila* embryo, a transient phase before cellularization, although other *Drosophila* tissues (e.g. muscle) form persistent multinucleate cells. These examples highlight how persistence, habitat, and ecological niche vary even among closely related taxa. The tree was visualized and annotated using the Interactive Tree Of Life (iTOL) v6[149].

or metabolites[34]. In some simple multicellular organisms, these bridges provide the structural basis for multicellular cohesion[35]. In choanoflagellate rosettes, for example, rapid intercellular calcium signaling occurs despite their colonial organization, reflecting substantial cytoplasmic communication among cells[36]. Conversely, multinucleate systems can show partial compartmentalization, such as the variable septation observed in fungal hyphae, where pore size and permeability differ across species and physiological states[37]. These observations suggest that multinucleation and multicellularity lie along a spectrum of cytoplasmic integration rather than being strictly discrete categories.

This review aims to explore the ecological and evolutionary roles of multinucleation, highlight the features that enable persistence of multinucleation across diverse niches, and examine the benefits and trade-offs of multinucleate versus multicellular strategies. By considering the cellular routes by which multinucleation forms and the underlying molecular machinery that enables it (Figure 2) and examining the environments in which multinucleation is advantageous (Box 1), we aim to identify general principles that unify multinucleate cells across the tree of life. Whether the repeated emergence of multinucleation reflects evolutionary robustness or whether it is better understood as a context-dependent solution that is readily gained and lost remains an open question. For now, we focus on what multinucleation demonstrably enables, and why understanding these systems illuminates broader questions about cellular organization, life-cycle evolution, and the diversification of complex life.

Box 1. Ecological niches favoring the evolution of multinucleation.

The ecological context in which an organism evolves strongly influences the development and persistence of multinucleate cells. Environmental factors such as nutrient availability, substrate structure and heterogeneity, and predation pressure impose selective constraints that can favor shared cytoplasmic organization. In such settings, multinucleation offers a versatile strategy for sustaining growth, coordinating metabolism, and maintaining resilience under fluctuating or resource-limited conditions.

Terrestrial ecosystems: Terrestrial ecosystems, particularly soils and decomposing organic matter, are physically complex and highly heterogeneous environments. Nutrients occur in patchy microhabitats, microbial communities are dense, moisture levels fluctuate, and substrates can be mechanically resistant. Organisms must navigate steep chemical gradients, shifts in hydration cycles, and episodic resource pulses. Together, these features create a mosaic landscape where growth depends on continually responding to local and rapidly changing conditions.

Aquatic ecosystems: Aquatic environments, both marine and freshwater, present a very different set of constraints. Water supports large, extended cell shapes but also exposes organisms to turbulence and to constantly fluctuating nutrient availability. Many habitats are oligotrophic; others are periodically mixed or disturbed by sediment flow. In addition, deep-sea settings involve high pressure, low temperatures, and chronic nutrient scarcity. Across these ecosystems, resource landscapes are shaped by fluid motion rather than substrate structure, and chemical signals disperse quickly, creating dynamic and often unpredictable conditions.

Intracellular niches: Intracellular parasitic niches are tightly enclosed, nutrient limited, and under constant immune surveillance. Within erythrocytes, hepatocytes, or algal cytoplasms, movement is restricted and resource access is finite. For example, parasites must replicate efficiently within a fixed space while avoiding detection, which, together with spatial confinement, strongly shapes how growth and division are organized in these environments.

Transitional and fluctuating niches: Some organisms occupy habitats that shift rapidly over space or time. Seasonal environments, transient substrates, dispersal phases, and transitions between aquatic and benthic zones all impose fluctuating conditions. In these settings, organisms often benefit from flexible life cycles capable of switching between different cellular architectures. Transitional niches also include stress-induced states, which can be triggered by desiccation, hypoxia, or chemical damage, in which cells temporarily reorganize their growth dynamics, nuclear behavior, or genome content.

Developmental contexts: Multinucleation also arises in developmental settings where rapid expansion, intense biosynthetic demand, or coordinated activity across large cellular domains is required. Early embryogenesis often involves rapid nuclear divisions before cellularization; specialized tissues must accumulate resources quickly; and contractile or absorptive epithelia rely on coordinated gene expression across extensive cytoplasmic territories. These developmental niches impose tight temporal constraints distinct from those experienced by free-living cells.

Unifying principles of multinucleation and their evolutionary significance

Multinucleation has arisen repeatedly across eukaryotes because it provides a set of powerful functional advantages that allow organisms to scale metabolism, regulate spatially distributed processes, coordinate activity across large cytoplasmic domains, and flexibly adjust their architectures in response to environmental and developmental demands. Although the organisms that use these strategies inhabit strikingly different ecological niches, each feature of multinucleation supports a shared underlying principle: distributing genomic, metabolic, or regulatory capacity across space enables cells to achieve levels of dynamic coordination and performance that could be difficult for uninucleate cells or conventional multicellular organization.

The cellular machinery enabling multinucleation is deeply conserved, drawing on core eukaryotic capacities involving cytoskeletal remodeling, vesicle trafficking, membrane fusion, and transcriptional regulation[15–21]. The recurrence of these mechanisms across independent lineages underscores the convergent nature of multinucleation as a versatile and efficient solution to the challenges of scale, coordination, and adaptation. Below, we articulate how each functional principle aligns with specific ecological or developmental contexts.

Enhanced biosynthetic capacity and transcriptional scaling

Changes in genome copy number can directly influence RNA and protein abundance[38,39], linking transcriptional output to cellular architecture and biosynthetic capacity. By increasing nuclear number, multinucleate cells amplify genomic and transcriptional output without the cost of constructing additional cell membranes or intercellular junctions[40,41]. Additionally, the distribution of multiple nuclei throughout the cytoplasm can permit localized gene expression, allowing different regions of the same cell to have distinct biosynthetic profiles. This spatial organization distinguishes multinucleation from polyploidy, in which transcriptional amplification remains confined to a single region.

The advantages of biosynthetic scaling are realized in strikingly different ecological and developmental contexts. In terrestrial fungi and plasmodial slime molds, dispersed nuclei support rapid expansion across heterogeneous substrates, fuel the metabolism required for extensive exploratory networks, and allow organisms to exploit resource hotspots[1,42–48]. In animals, myonuclei positioned along the length of a muscle fiber enable localized transcriptional responses and maintain the high protein turnover required for contractility and regenerative capacity[33,49,50]. For siphonous algae like *Caulerpa* and *Bryopsis*, which are multinucleate giant cells that inhabit nutrient-poor and mechanically demanding marine environments, multinucleation provides the biosynthetic capacity necessary to support their remarkable macroscopic growth[11,51–54]. Despite their ecological differences, these systems illustrate the same core principle: scaling biosynthesis through nuclear multiplication allows organisms to match metabolic output to environmental opportunity, whether for growth or structural maintenance.

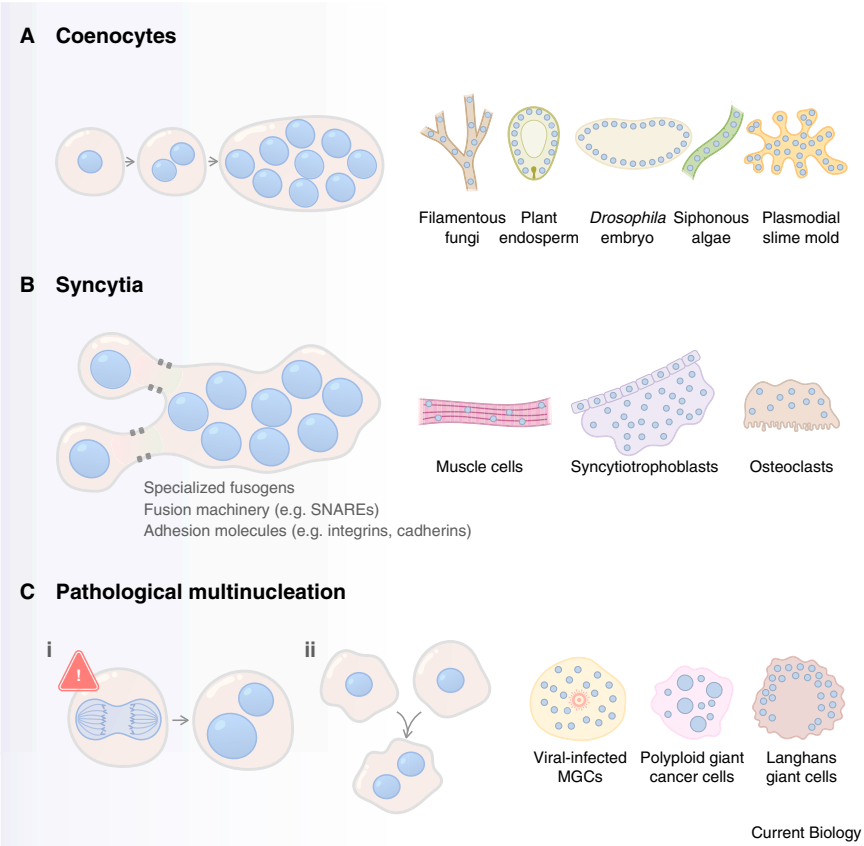

Figure 2. Mechanisms and dynamics of multinucleation across eukaryotes.
Multinucleation arises through multiple cellular processes that generate shared cytoplasmic domains containing multiple nuclei. Three principal routes are illustrated. (A) Nuclear division without cytokinesis (coenocytic growth) occurs when this division proceeds while cytokinesis is delayed or absent, producing many nuclei within a continuous cytoplasm. This mechanism enables rapid amplification of nuclear number and scaling of biosynthetic capacity with cytoplasmic volume and occurs in diverse lineages, including filamentous fungi[45,150,151], plant endosperm[7,152–154], plasmodial slime molds[79,155–157], siphonous algae[11,51,97], and early insect embryos such as the *Drosophila* blastoderm[130,131]. (B) Cell–cell fusion (syncytium formation) generates multinucleate cells through the fusion of individual uninucleate cells mediated by fusogens such as Myomaker/Myomerger, adhesion proteins such as integrins or cadherins, and cytoskeletal remodeling. Examples include skeletal muscle fibers[13,158], placental syncytiotrophoblasts[67,159], and macrophage-derived osteoclasts or multinucleated giant cells[160,161]. (C) Pathological multinucleation can arise from failed mitotic exit or cytokinesis, stress, or infection, producing multinucleated cells associated with genomic instability or tissue dysfunction. (i) Failed cytokinesis or aberrant mitotic exit results in a binucleated or polyploid daughter cell. (ii) Cell–cell fusion, driven by viral infection or pathological stress, generates multinucleate giant cells (MGCs). Examples include virus-induced syncytia, polyploid giant cancer cells, and Langhans giant cells[22–24,162–166].

Distributed spatial regulation within a shared cytoplasm

A defining challenge of cellular scaling is maintaining spatial control in the absence of internal partitions[55]. Large cells, regardless of nuclear quantity, must coordinate gene expression, translation, and signaling across extended cytoplasmic territories. Multinucleation does not eliminate this constraint but has the potential to circumvent it. By distributing nuclei throughout the cytoplasm, transcriptional capacity becomes decentralized, often reducing the need for long-distance transport of newly synthesized transcripts as multiple local transcriptional hubs emerge.

With advancements in single-nucleus RNA-sequencing (snRNA-seq) as well as spatial transcriptomics[56], researchers have gained more insights into the transcriptional states of nuclei in multinucleate cells. Recent work suggests that nuclei within a shared cytoplasm can differ substantially in transcriptional state. For example, in human placentas, dynamic heterogeneity and distinct developmental programs among nuclei within syncytiotrophoblasts were revealed using snRNA-seq and ATAC-seq[57]; in the slime mold *Physarum polycephalum*, individual nuclei display heterogeneous transcriptional states, suggesting they process local signals to coordinate growth, metabolism, and reproduction across the shared cytoplasm[32]; in vertebrate muscle cells, distinct nuclear subtypes exist in both uninjured and regenerating muscle[33]; and in filamentous fungi, expression profiles of nuclei vary between the periphery and center of *Aspergillus niger* colonies[58].

In addition to regulatory networks, biophysical factors such as nuclear positioning, cytoplasmic flows, and local cellular geometry can also shape transcriptional activity, suggesting that spatial organization can also contribute to gene expression heterogeneity. Microtubule-based forces help maintain nuclear spacing and positioning, coordinating cell-cycle progression and spatial independence, as reported in *Drosophila* embryos, the ichthyosporean *Sphaeroforma arctica*, and *Ashbya gossypii* fungi[15,59,60]. These findings raise the possibility that multinucleate cells may exhibit forms of ‘local individuality’, where distinct nuclear domains operate semi-independently while still contributing to collective cellular function[61,62].

Even with distributed nuclei and heterogeneous transcriptional profiles, spatial control extends beyond transcription. RNA-binding proteins and localized translation remain essential for coordinating protein synthesis in space and time. In *Ashbya gossypii*, condensates dependent on the RNA-binding protein Whi3 position specific mRNAs near growth zones, linking nuclear division to polarized growth[63,64]. Similar principles are at play in diverse systems, where localized translation limits selective protein synthesis to defined cytoplasmic regions[65], a strategy conserved from fungi to mammals and essential for cell-cycle control and polarity[63,66]. Thus, multinucleation alleviates some scaling constraints by decentralizing transcriptional activity, but it does not alone remove the need for other spatial regulatory mechanisms; instead, it enables an additional layer of organizational control.

Post-translational modifications further contribute to spatial regulation by modulating protein activity. Phosphorylation, ubiquitination, glycosylation, and SUMOylation rapidly modulate protein stability or function in response to local signals. In multinucleate syncytiotrophoblasts, for instance, growth factors such as insulin-like growth factor and leukemia inhibitory factor integrate MAPK/ERK and JAK/STAT signaling to coordinate proliferation and differentiation[67]. Together, these mechanisms illustrate how multinucleate cells maintain different levels of regulatory control across differing regions of cytoplasm.

Active transport and circulation in large, continuous cells

As cells increase in size, diffusion alone is not sufficient to sustain metabolic homeostasis[68]. Some multinucleate systems can reduce reliance on long-range movement of certain gene products, as described above, but multinucleation alone does not eliminate the physical limitations imposed by increased cytoplasmic scale. Large multinucleate cells must still transport metabolites, organelles, proteins, and signaling molecules over sizable distances. These challenges are met by coupling cytoskeletal networks to cytoplasmic streaming, enabling long-range movement within a continuous cytoplasm[69–71]. In this respect, parallels can be drawn between multinucleate cells and large polarized uninucleate cells, such as neurons, which utilize motor-driven transport along cytoskeletal tracks; however, unlike actomyosin-based bulk flow, microtubule-based kinesin and dynein motors are used for highly directional cargo delivery[72].

The benefits of long-range transport in multinucleate cells are evident in many contexts: in siphonous algae, such as *Caulerpa*, *Bryopsis*, and *Halimeda*, where actomyosin-driven streaming moves resources across macroscopic thalli[10,11,52,53,70]; in *Physarum* multinucleate plasmodia, where rhythmic contractions generate oscillatory flows that couple nutrient transport with signaling dynamics over extraordinary distances[71,73,74]; and in xenophyophores and other deep-sea foraminifera, where active transport maintains homeostasis under nutrient-poor, low-temperature, and high-pressure conditions[4,75–78]. Such active circulation systems enhance metabolic efficiency and extend cellular function beyond the limits of passive diffusion.

Thus, multinucleation does not bypass the biophysical limits of size, but instead reworks how those limits are managed. While transcription may become locally specialized, transport and coordination require more generic solutions. The success of multinucleate architectures, therefore, depends not only on nuclear numbers but also on the evolution of robust intracellular transport systems to overcome limitations of scale.

Flexibility across life-cycle transitions

Many organisms in multinucleate lineages alternate between uninucleate and multinucleate stages, giving them the ability to reorganize their growth and reproductive strategies in response to environmental conditions. This flexibility buffers against environmental fluctuations, such as nutrient scarcity, desiccation, and host limitation, or aids in dispersal and niche establishment. *Physarum* transitions between uninucleate amoebae and multinucleate plasmodia depending on nutrient availability[79,80]; parasites such as *Plasmodium* spp. generate multinucleate stages to maximize progeny within hosts or host cells before generating invasive uninucleate stages[81,82]; and ichthyosporeans, such as *Sphaeroforma arctica*, undergo coenocytic growth (Figure 2A) prior to cellularization and dispersal[5,60]. Fungi likewise alternate between multinucleate hyphae and uninucleate spores during stress or reproductive transitions[45,83]. Similar ecological switching occurs in the amoeba *Clautriavia*, which forms large multinucleate coenocytes when food is abundant but reverts to uninucleate cells that divide by binary fission as resources become scarce[84]. In each case, this capacity to alternate between uninucleate and multinucleate forms allows organisms to balance resilience, reproduction, and resource use across fluctuating environments.

Energetic considerations of cytoplasmic continuity

Multinucleation may offer an energetically efficient route to building and maintaining large or spatially complex cellular architectures. Here, energetic costs refer to the metabolic investment required to construct and maintain cellular structures such as membranes and junctions, as well as the biophysical costs associated with transporting molecules and maintaining homeostasis across large cytoplasmic distances[85]. Membrane biogenesis and the maintenance of electrochemical gradients across cellular boundaries carry substantial ATP costs[86]. By expanding a shared cytoplasm rather than dividing it, multinucleate systems may bypass a portion of these costs, avoiding the need to build and maintain membranes, junctions, and the intercellular signaling machinery needed to coordinate activity across cell boundaries[40,86].

While the energetic consequences of this organization are not fully resolved across all lineages, several biological systems illustrate how reduced compartmentalization can coincide with large-scale growth or efficient resource allocation. In aseptate fungal lineages such as Mucoromycota and Glomeromycota, extensive multinucleate networks traverse heterogeneous substrates and fluctuating nutrient microhabitats. Cytoplasmic continuity enables bulk streaming that distributes nutrients and organelles across the network with lower hydraulic resistance than transport across sequential cellular compartments[83,87]. Many Glomeromycota form arbuscular mycorrhizal symbioses with over 80% of terrestrial plants, where multinucleation facilitates nutrient exchange with hosts and redistribution within the fungal network[42,43,88–90]. Siphonous algae similarly achieve macroscopic morphologies as single multinucleate cells, with continuous cytoplasm supporting rapid transport and flexible redistribution of resources across the thallus[91,92]. Deep-sea xenophyophores take this further, achieving vast coenocytic cell sizes while restricting metabolically active cytoplasm to a small fraction of the total cell volume, with the remainder occupied by metabolically inert or waste material, including barite crystals and stercomare[93]. This spatial restriction of metabolism, combined with the avoidance of the membrane and junction costs that come with multicellular organization, could be interpreted as key energetic adaptations to extreme deep-sea conditions[93].

Managing cytoplasmic continuity, however, comes with tradeoffs. While energetically advantageous in some respects, such continuity also introduces barriers or vulnerabilities. Achieving and maintaining cytoplasmic continuity via fusion (Figure 2B) requires overcoming a considerable biophysical barrier — cell surface crowding by glycoproteins[94]. Furthermore, without internal partitions, damage to one region of the cell can propagate through the shared cytoplasm. Many multinucleate systems have therefore evolved mechanisms to mitigate these risks. In

ascomycetes, such as *Aspergillus nidulans*, *Trichoderma atroviride*, and *Neurospora crassa*, septal pores can be rapidly occluded by Woronin bodies, peroxisome-derived organelles that seal damaged compartments and prevent cytoplasmic leakage[95,96]. Siphonous algae similarly deploy rapid wound-response mechanisms, including plug formation and cytoskeletal rearrangements, to seal damaged regions despite the absence of cellular boundaries[51,52,54,97]. Together, these examples suggest that cytoplasmic continuity offers a low-cost solution to scaling, but at the price of increased vulnerability, a constraint that multinucleate systems mitigate through mechanisms that safeguard the integrity of the shared cytoplasm. The same cytoplasmic continuity can also constrain functional specialization, given that streaming and diffusion tend to homogenize cellular contents, such that in some ecological or functional contexts, other scaling strategies may offer a more effective solution.

Multinucleation and multicellularity as alternative scaling strategies

Multinucleation and multicellularity represent two distinct yet functionally overlapping solutions to the problem of biological scale. Multinucleate cells internalize the collective, housing many nuclei within a continuous cytoplasm, while multicellular organisms externalize it, distributing nuclei across discrete but coordinated cells. In many lineages, they coexist or alternate across life cycles as both achieve division of labor, metabolic efficiency, and coordinated behavior, albeit to different extents[27,98,99].

Multinucleate architectures

Multinucleate organization achieves multicellular-like integration without constructing membranes between nuclei or relying exclusively on intercellular signaling. These cells can coordinate activity across large spatial domains and redistribute resources rapidly. Continuous cytoplasm also allows signals, organelles, and metabolites to move freely, supporting cohesive behavior across regions that would otherwise require complex intercellular communication and intercellular transport structures. However, this architecture is not without costs. As cytoplasmic volume increases, diffusion becomes limiting, placing greater demands on active transport systems. Maintaining order across a large, continuous cell requires precise regulation of nuclear activity, cytoskeletal organization, and spatial patterning. Local disturbances, such as infection, can propagate more readily through a shared cytoplasm than in multicellular tissues. Despite these trade-offs, there are specific ecological niches where multinucleation excels, including heterogeneous substrates that require long-range foraging, mechanically strenuous environments, or intracellular niches for immune evasion (Box 1). In such contexts, the ability to integrate many nuclei within one continuous cytoplasm offers a robust and adaptable solution to challenges that might be difficult for either uninucleate cells or fully partitioned multicellular tissues to meet.

Simple multicellular architectures

Simple, facultative multicellular architectures, such as colonial and aggregative forms, by contrast, preserve individuality while achieving collective behavior. Independent cells interact through adhesion and chemical signaling, forming transient assemblies that can readily form or dissipate in response to environmental cues. In choanoflagellates, bacterial lipids induce clonal rosette formation[100]; and in *Dictyostelium*, starvation triggers chemotaxis-driven aggregation reinforced by kin recognition, the ability to recognize genetically similar individuals, and policing, mechanisms that suppress the selfish behavior of other individuals[101]. Such collectives can reduce predation, as seen in *Phaeocystis* mucilaginous colonies, while enhancing resource capture[102,103]. These systems are flexible and facilitate cooperation without permanent commitment[104]. Their limitations lie in slower and less precise coordination, mechanical fragility, and vulnerability to cheaters (individuals that exploit shared resources without contributing to their production), yet they thrive in fluctuating or resource-limited environments where reversible collectives offer adaptive advantages.

Complex multicellular architectures

Complex multicellular architectures, meanwhile, allow cooperation through stable connections and differentiation, producing tissues composed of specialized cell types integrated by signaling networks. This strategy supports deep functional specialization, robust homeostasis, and the capacity for complex, scalable body plans[105–108]. However, these benefits come at a high energetic cost: maintaining intercellular communication and tissue integrity may slow reproduction, increase energy expenditure to construct such tissues, and reduce reversibility once cells are terminally differentiated[40]. Consequently, we can speculate that multicellularity dominates in relatively stable, structured habitats where the benefits of long-term specialization outweigh the flexibility lost through commitment[109].

Evolutionary convergence in organizational strategies

Together, these architectures illustrate that evolution repeatedly converges on a set of solutions to the same fundamental challenges, e.g. scaling, coordination, and conflict mediation, each balancing autonomy and integration in distinct ways[99,108,110]. Multinucleation likely achieves flexibility by connecting processes in a unified cytoplasm[81,111]; colonial systems favor adaptability through loose cooperation[103]; and multicellularity establishes stability through division of labor[34]. These possibilities remain hypotheses, and comparative work will be essential to test how these organizational strategies truly differ in function and constraint. Nonetheless, their recurrence and coexistence across lineages reveal a shared evolutionary logic: the drive to extend the reach of cooperation without forgoing control (Figures 1 and 3).

Phylogenetic distribution of multinucleation and multicellularity

It is striking that multinucleation is found almost exclusively in eukaryotic lineages that also evolved some form of multicellularity, either simple (facultative) or complex (obligate) (Figure 1 and Table S2). This co-occurrence suggests that the underlying cellular toolkits required for coordinating multiple nuclei may overlap with those needed for coordinating multiple cells, potentially predisposing certain lineages to both architectures[98,106,107] (Figure 3). Even groups dominated by unicellular species, such as the Discoba, show this dual potential: *Acrasis kona* exhibits an aggregative life stage capable of collective behavior, while *Multisulcus malaysiensis*, another discobid, can produce multinucleate cells[112,113]. Putative multinucleate and simple multicellular stages have also been reported in breviates and apusomonads, suggesting that these lineages warrant further

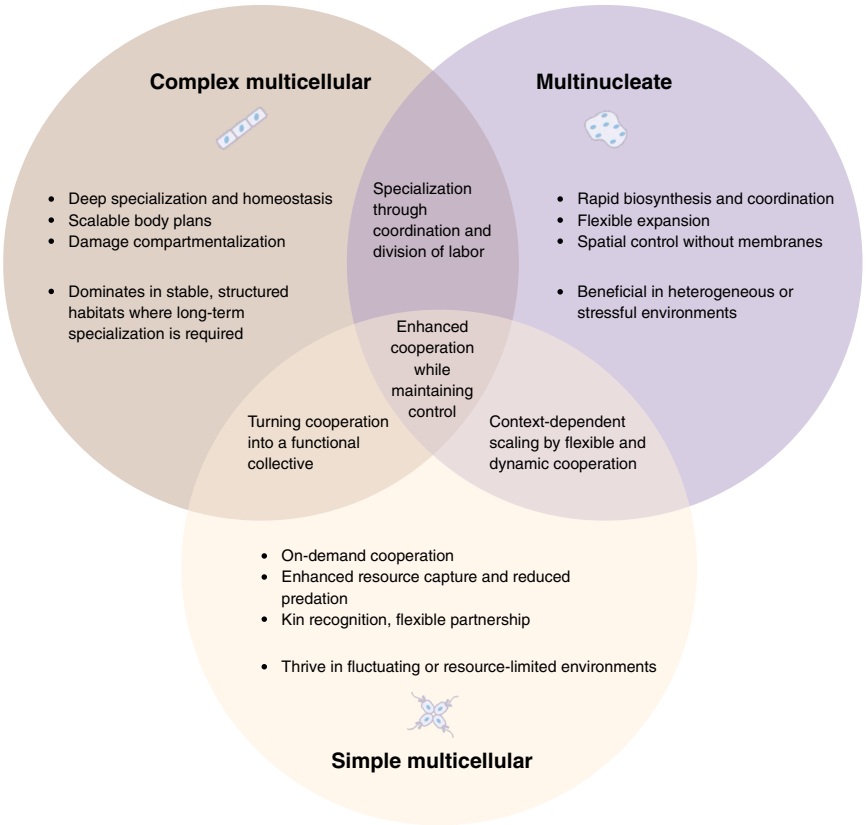

Figure 3. Conceptual relationships among multinucleate and multicellular organizational strategies.

The Venn diagram summarizes the shared and distinct principles of three major eukaryotic organizational structures that solve problems of coordination and scaling in different ways. Multinucleate cells integrate multiple nuclei within a continuous cytoplasm, achieving rapid coordination and regionalized function. Complex multicellular organization achieves long-lasting cooperation through stable adhesion, developmental patterning, and division of labor, enabling specialization. Simple multicellularity maintains individuality while coordinating behavior through reversible adhesion and signaling, allowing flexible responses to environmental fluctuations. Overlapping regions highlight convergent strategies: enhanced cooperation while maintaining internal control, specialization through coordinated division of labor, and context-dependent scaling via dynamic cooperation.

investigation to clarify how they fit within the broader landscape of cellular organization[114,115].

There are a few notable exceptions, however. In Metamonada, which includes diplomonads such as *Giardia duodenalis*, multinucleation occurs despite an apparent lack of multicellular forms; the characteristic binucleate state of diplomonads represents a minimal yet genuine multinucleate organization[116]. The trichomonads, e.g. from the genus *Gyronympha*, are also multinucleated, composed of clusters of karyomastigonts, which are flagella-associated nuclei[117]. This deviation from the broader pattern raises interesting questions about why multinucleation can evolve in the absence of multicellularity in this lineage. Additionally, it appears that there are only two lineages, Haptophyta and Glaucophyta, that form simple multicellular structures but seem to lack multinucleate cells. The haptophyte *Phaeocystis*[102,103] and the glaucophyte alga *Cyanoptyche gloeocystis*[118] both form colonies. Interestingly, a close relative of the haptophytes, the centrohelid *Raphidiophrys heterophryoidea*, can form both multinucleate and simple multicellular aggregates, and there is speculation as to whether similar polymorphisms can be observed in haptophytes as well[119]. Together, these exceptions point to important gaps in our understanding and highlight avenues of exploration to test which cellular features enable or constrain these cellular architectures.

Unresolved relationships between multinucleation and multicellularity

Whether multinucleation precedes, parallels, or follows multicellularity remains to be resolved[27,120,121]. Both enable coordination and division of labor, yet through contrasting architectures: one continuous, the other compartmentalized. Multinucleation may have served as a functional precursor to multicellularity, allowing spatial patterning to emerge within a shared cytoplasm before the emergence of intercellular junctions. Alternatively, the molecular toolkits for multicellular coordination may facilitate the emergence of multinucleation as a derived trait. Understanding this relationship offers insight into one of life's major evolutionary transitions.

Where multinucleate states arise through fusion events, their relationship to multicellularity is potentially derived rather than ancestral. Formation of syncytia (Figure 2B), such as syncytiotrophoblasts and skeletal muscle fibers, depends on adhesion proteins like cadherins[122,123], which themselves can be traced back to the earliest holozoans. Choanoflagellates already encode cadherins, C-type lectins, and tyrosine kinases[124], which could suggest that the molecular toolkits for cell–cell adhesion and communication predate animals and were later co-opted for syncytial fusion. By contrast, coenocytic multinucleation, arising from nuclear division without cytokinesis (Figure 2A), may offer a more direct route to multicellularity, bypassing adhesion-based mechanisms but utilizing other shared mechanisms that rely upon microtubules or actin reorganization, for example. Notably, ichthyosporeans, close unicellular relatives of animals, display coenocytic growth phases in which nuclei divide synchronously within a shared cytoplasm before cellularization[5,60,125,126] (Figure 4). In this regard, multicellularity may represent a reconfiguration of coenocytic multinucleation, in which a continuous cytoplasm containing multiple nuclei became progressively partitioned into discrete, interacting cells.

Multinucleation and multicellularity may not represent successive stages of complexity but parallel solutions to the problem of organizing multiple genomes and their outputs within a coherent biological unit. Consistent with this view, transitions occur in both directions. In fungi, comparative analyses suggest that

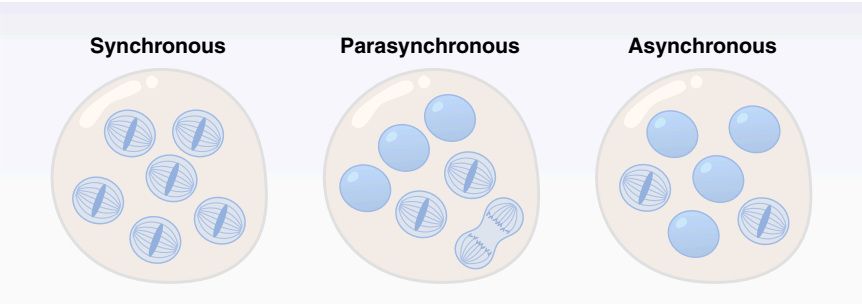

Figure 4. Dynamics of nuclear division in multinucleate cells.
Multinucleate cells exhibit diverse nuclear-division dynamics, with varying degrees of synchrony. When nuclei divide synchronously within a multinucleate cell, all nuclei enter mitosis simultaneously under shared cytoplasmic control, typically coordinated by common regulatory factors (as occurs, for example, in early *Drosophila* embryos[131]). With parasynchronous nuclear divisions, mitotic waves propagate through the cytoplasm of the multinucleate cell, resulting in a partial coupling between nuclear cycles within nearby regions of the cytoplasm (as seen in *Aspergillus nidulans*[151]). Asynchronous divisions are characterized by only a subset of nuclei dividing at a given time, reflecting potential locally regulated control of cell-cycle progression and generating heterogeneity in nuclear states (as seen in *Plasmodium falciparum*[81,82]). Experimental and observational evidence suggests that asynchronous dynamics can distribute energetic demand across time and space and become more prevalent under conditions of metabolic stress[2,111,150,167]. Together, these modes illustrate how multinucleate cells balance global coordination with local autonomy to regulate nuclear activity within a shared cytoplasm.

multicellular architectures evolved from ancestrally multinucleate hyphal systems through the progressive acquisition of septa and compartmentalization[127]. Conversely, several syncytial tissues in animals evolved from multicellular ancestors: skeletal muscle fibers form through myoblast fusion[128], the mammalian syncytiotrophoblast arises through repeated trophoblast fusion[129], and insect embryos develop from a multinucleate blastoderm prior to cellularization[130,131]. The selective pressures driving these transitions likely included enhanced integration of cellular responses, accelerated growth, and faster patterning, advantages particularly evident where syncytia support rapid, coordinated electrical signaling. The trabecular syncytium of glass sponges propagates fast action potentials across the body despite the absence of a nervous system[132], and the recently described syncytial nerve nets of ctenophores suggest that cytoplasmic continuity can underpin integrated neural responses even in early-diverging lineages[133].

An unresolved question is why syncytial architectures evolve at all, given that they require cells to first undergo cytokinesis only to later fuse again, and that fusion itself also requires overcoming substantial biophysical barriers[94]. One possibility is that fusion represents an evolutionarily accessible route to cytoplasmic continuity once uninucleate organization reaches a local fitness maximum[134]; rather than remodeling the cell-division machinery itself, fusion co-opts existing membrane merger pathways to achieve a similar outcome. The fact that this apparently circuitous and costly route to multinuclearity is repeatedly favored across animal lineages underscores the magnitude of the functional advantages, particularly speed and coordination. Although recurrent, the molecular routes to fusion differ strikingly. The syncytiotrophoblast, for example, evolved convergently across placental mammals through repeated co-option of endogenous retroviral envelope proteins (syncytins)[135], while the skeletal muscle fusogens Myomixer and Myomaker arose *de novo* and by gene duplication, respectively[128], illustrating that there is no single molecular mechanism controlling cell–cell fusion. These observations invite further comparative study into the molecular and physical bases of large-scale coordination across eukaryotes.

Mitotic mechanisms and the evolution of cellular architectures

Because multinucleate cells must coordinate multiple nuclear cycles within a shared cytoplasm, mitotic mechanisms in these cells likely influence or are influenced by cellular architecture. If multinucleation and multicellularity represent parallel routes to large-scale coordination, the diversity of mitotic mechanisms offers a window into how these architectures evolved. Across eukaryotes, mitosis tends to align with cellular organization, where multinucleate lineages predominantly exhibit closed mitosis, in which the nuclear envelope remains intact, and uninucleate lineages favor open mitosis, involving nuclear envelope breakdown[136–139]. Closed mitosis allows multiple spindles to operate independently within a shared cytoplasm, preserving local control amid cytoplasmic continuity. In contrast, open mitosis facilitates stronger coupling between nuclear and cytoplasmic processes, an arrangement well suited to uninucleate cells.

Intriguingly, some lineages retain the capacity for both types of mitosis. *Physarum*, for instance, performs open mitosis in its uninucleate amoebal form but closed mitosis in its multinucleate plasmodial form[79,80]. This dual capacity within a single organism highlights how mitosis can evolve contextually, depending on life-cycle stage and cellular organization. The ability to accommodate both open and closed mitosis may have facilitated evolutionary transitions between uninucleate, multinucleate, and multicellular states, linking the mechanisms of division to the broader challenge of organizing genomes or cells in space and time.

Challenging the notion of individuality

Multinucleate cells challenge the view of the uninucleate cell as the fundamental unit of life, revealing that biological individuality can emerge at multiple organizational levels. Selection may act on individual nuclei (genetically identical or distinct), on specific cytoplasmic domains, or on the organism as a whole. This multilevel perspective parallels discussions in evolutionary biology about individuality in colonial organisms, holobionts, and symbiotic systems[27,105,108,140–143].

When genetically distinct nuclei coexist in a shared cytoplasm, as in fungal heterokaryons, cooperation and conflict become central concerns. Such chimeric states can persist for long periods, raising questions about how selection operates within a shared cytoplasm and how policing mechanisms suppress selfish nuclear lineages that might otherwise exploit communal resources. Various control strategies have been reported to

suppress such conflicts, including: selective nuclear degradation, in which incompatible nuclei are targeted for programmed destruction[144]; compartmentalization through septal plugging, which isolates heterokaryotic cells and prevents the spread of incompatible nuclei[145]; and nucleophagy under starvation, whereby specific nuclei are degraded to redistribute nutrients and ensure colony survival[90]. Together, these mechanisms restrict access to shared cytoplasmic goods and maintain cooperative function within multinucleate cells[110,111,146,147].

Not all nuclear heterogeneity arises from genetic differences. Nuclei in multinucleate cells can divide asynchronously (Figure 4), occupy distinct transcriptional states, and respond differently to local signals despite sharing cytoplasm[1,45,81,148]. This nuclear autonomy enables regional specialization, localized mRNA gradients, spatially restricted translation, and the formation of subcellular zones with distinct physiological functions. Such internal patterning demonstrates that discrete cellular partitions are not necessary for spatial complexity.

Conclusions

Multinucleate cells are more than biological anomalies; they are recurrent, versatile solutions to fundamental problems of scale, coordination, and adaptability. Spanning the tree of life, from deep-sea protists to developing embryos and intracellular parasites, they compel us to reconsider multinucleation as a robust strategy for growth, resilience, and survival. By enabling distributed control, spatial compartmentalization without partitions, and rapid scaling of transcriptional capacity, multinucleation redefines where the line between a single cell and a collective truly lies.

This makes multinucleate systems uniquely powerful for exploring cooperation and conflict at the subcellular level, testing theories of individuality and evolution, and uncovering organizational principles that illuminate eukaryotic origins to modern biotechnological design. Emerging tools now make it possible to interrogate these questions with unprecedented precision: live imaging and spatial transcriptomics reveal nuclear dynamics in real time, single-nucleus sequencing and multi-omics profiling resolve heterogeneity within a shared cytoplasm, and quantitative modeling and synthetic reconstruction can experimentally test how coordination emerges among many genomes.

Together, these advances promise to transform our understanding of multinucleate life, not merely as a cellular curiosity, but as a window into the general principles of biological organization. As we begin to investigate and understand these systems in molecular detail, we are invited to rethink not only how cells function, but what it means to be a cell in the first place.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

Supplemental information including two tables can be found with this article online at https://doi.org/10.1016/j.cub.2026.03.066.

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