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Did axons evolve by activating cytokinesis during interphase? A hypothesis on the origin of neurons

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ABSTRACT **Although synaptic evolution has been extensively studied, how axons first arose remains unexplored. Because evolution often occurs by coopting existing features, we review the evolutionary histories, biophysics, and cell biology of cytokinesis, cell crawling, and ciliogenesis to explore the origin of axons. Although we found that cilia and axons are outwardly similar, and growth cones strongly resemble the leading edge of crawling cells, the biophysical processes and the critical proteins that drive each seem weakly linked to axons as a structure. In contrast, the traction force machinery that pulls daughter cells apart during cytokinesis and the cytoskeletal organization of cytokinetic bridges appear to have a one-to-one correspondence to neuronal growth cones and axons. Based on these observations, we propose the hypothesis that axons evolved due to mutations that partially activated cytokinesis in an interphase cell. To rigorously test this hypothesis, we suggest conducting systematic phylogenetic analysis of the genes essential for each process, paired with molecular genetic studies in which critical genes are systematically disrupted. Doing so will provide a framework for understanding the relationship between diverse cellular processes, the early evolution of neurons, and insights that could potentially assist in treating cancer and promoting neuronal regeneration.**

SIGNIFICANCE STATEMENT

- This work opens new avenues for discussion of the evolutionary relationships between cytokinesis, ciliogenesis, amoeboid migration, mesenchymal migration, neuronal migration, dendritic elongation, and axonal elongation.
- Pursuing the question of how axons evolved may help answer whether neurons in all metazoans share a single origin or arose independently as the result of convergent evolution.
- Understanding the evolutionary connections between axonal elongation, cell crawling, and cell division may lead to better treatments for cancer and neuronal injury that minimize potential side effects.

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Abbreviations used: APC, adenomatous polyposis coli; aPKC, atypical protein kinase C; ARMC9, armadillo repeat containing 9; ARP2/3, actin-related protein 2/3; c-Src, cellular sarcoma; cAMP, cyclic adenosine monophosphate;

INTRODUCTION

Although the evolution of synaptic transmission has been extensively explored (Kristan, 2016; Burkhardt, 2022; Sachkova, 2024), the question of how axons, as structural entities, first evolved has received surprisingly little attention. This is notable because the axon's ability to rapidly transmit signals over long distances is a striking and unique feature of neurons. More broadly, fundamental questions remain about when neurons first appeared and in what types of organisms (Budd and Jensen, 2017; Arendt *et al.*, 2019; Paulin and Cahill-Lane, 2021). Challenges to resolving these questions include the absence of universal molecular markers for neurons across metazoans and recent updates on the early branching order of metazoan lineages (Schultz *et al.*, 2023; Sachkova, 2024). Consequently, interesting questions emerge, such as whether neurons in ctenophores (comb jellies) are homologous to those in bilaterians, such as humans (Figure 1A). Because axons are a defining feature of neurons, insights into how these structures evolved may help resolve this and other long-standing questions. Building on the principle that evolution often proceeds by modifying preexisting features, we consider four hypothetical evolutionary pathways that could give rise to axons (Figure 2).

Modified cytokinesis

Because many cytokinesis-related genes are essential for axon outgrowth (Baas, 1999; Pollarolo *et al.*, 2011; Lu and Gelfand, 2017), and like axons, cytokinetic bridges that form between daughter cells at the end of mitosis also have bundled microtubules surrounded by a spectrin/actomyosin meshwork (Dubey *et al.*, 2020; Sobral *et al.*, 2021), neurons may have evolved as the result of partially inducing cytokinesis in an interphase cell. Here, growth cones would be evolutionarily homologous (i.e., sharing a common evolutionary origin) to the traction force-generating polar regions of dividing cells (Lamoureux *et al.*, 1989; Burton and Taylor, 1997), and the axon would be homologous to the cytokinetic bridge.

Modified cell crawling

Based on the molecular overlap and structural commonalities between growth cones and crawling cells (Miller and Suter, 2018; Dogterom and Koenderink, 2019), axons may have evolved due to mutations that caused a small region of the neuronal cell body to activate cell migration machinery. As a result, this region moved away from the cell body to form an axon. Here, growth cones would be homologous to crawling cells, and the axon shaft would have initially been a simple extension of the cell body, which later acquired its distinctive components.

Modified ciliogenesis

Because axons resemble eukaryotic cilia/flagella in that both are long, thin structures built from microtubules that depend on robust transport mechanisms to lengthen, they may have initially evolved through the modification of the cilia assembly pathway (Carvalho-Santos *et al.*, 2011; Khan and Scholey, 2018). Although cilia elongate through a specialized set of proteins (Reynolds *et al.*, 2018), the acquisition of cell crawling machinery at its tip would allow it to extend in a directed manner based on guidance cues generated by other cells. Here, the axon shaft would be homologous to a cilium.

De novo evolution

Alternatively, instead of axon outgrowth being a modification of a preexisting pathway, it may have evolved through a novel but currently unknown set of molecular innovations. An excellent example is seen in the evolution of major sperm protein in nematodes, which generates a unique form of cell crawling that does not involve actin (Roberts and Stewart, 2000; Fritz-Laylin, 2020). If so, outward similarities between axons and other cellular features would have arisen through convergent evolution, as is seen with bacterial and eukaryotic flagella.

With this framework, we discuss the biophysical and molecular relationships between cytokinesis, ciliogenesis, various forms of cell motility, and axon outgrowth to outline possible evolutionary pathways leading to axons. To evaluate these hypotheses, we first review the evolutionary origin of the core machinery supporting neuronal function and axon outgrowth.

RESULTS

Modern synaptic transmission machinery powered cytokinesis in the last eukaryotic common ancestor

Modern bilaterian neurons possess a unique constellation of features, including neurotransmitters, microtubule-based vesicular transport, exocytosis, endocytosis, and actin-based traction force generation. Nonetheless, these features arose as genetic innovations early in the evolution of eukaryotic cells to support other cellular processes (Figure 1A). In particular, essential components of the microtubule-based transport machinery (color-coded in blue) needed for neuronal function were present in the last eukaryotic common ancestor (LECA) (O'Malley *et al.*, 2019). Likewise, genes essential for contractile force generation and cell adhesion in neurons (color-coded in red) evolved before the *Amoebozoa* lineage diverged from the rest of Eukaryota (Figure 1B). Because our goal here is to evaluate the hypothesis that axons evolved by repurposing molecular machinery that was initially used for another cellular process, we start by considering what neuronal genes were present in early eukaryotic cells and their initial cellular role.

Although one might imagine the LECA to be a "primitive" cell, phylogenetic studies suggest it was a remarkably sophisticated protist (Figure 1A) (Garg and Martin, 2016; Bremer *et al.*, 2023).

CAMSAP, calmodulin-regulated spectrin-associated protein; Cdc20, cell division cycle 20; Cdc42, cell division cycle 42; Cdh1, cadherin-1 (E-cadherin); CDK1, cyclin-dependent kinase 1; CDK5, cyclin-dependent kinase 5; CEP104, centrosomal protein 104; CHE12, chemosensory defective 12; CLASP, cytoplasmic linker associated protein; CRISPR/CAS9, clustered regularly interspaced short palindromic repeats / CRISPR-associated protein 9; DCC, deleted in colorectal cancer; EB1, end binding protein 1; ECM, extracellular matrix; Ect2, epithelial cell transforming sequence 2 oncogene; EGF, epidermal growth factor; ESCRT-III, endosomal sorting complex required for transport III; FAK, focal adhesion kinase; FAP256, flagellar associated protein 256; G1, phase Gap 1 phase of cell cycle; G2, phase Gap 2 phase of cell cycle; GAPs, GTPase activating proteins; GEFs, guanine nucleotide exchange factors; GO, gene ontology; GTPases, guanosine triphosphatases; IFT, intraflagellar transport; LACA, last amorphean common ancestor; LECA, last eukaryotic common ancestor; LMCA, last metazoan common ancestor; MAP2, microtubule-associated protein 2; MAPs, microtubule-associated proteins; MgcRacGAP, male germ cell rac GTPase-activating protein; MTOC, microtubule organizing center; NDEL1, nuclear distribution element-like 1; NGF, nerve growth factor; NMII, non-muscle myosin II; p16INK4a, cyclin-dependent kinase inhibitor 2A; p27Kip1, cyclin-dependent kinase inhibitor 1B; Par1/MARK, partitioning-defective 1 / microtubule affinity-regulating kinase; Rac, ras-related C3 botulinum toxin substrate; Ran, ras-related nuclear protein; Rap, ras-related protein rho; Ras, homologous RhoGEF; Rho, guanine nucleotide exchange factor; RNAi, RNA interference; ROCK, Rho-associated, coiled-coil containing protein kinase; SCAR, suppressor of cyclic AMP receptor; SNARES, soluble NSF attachment protein receptors; TPX2, targeting protein for xenopus kinesin-like protein 2; WASP, wiskott-aldrich syndrome protein.

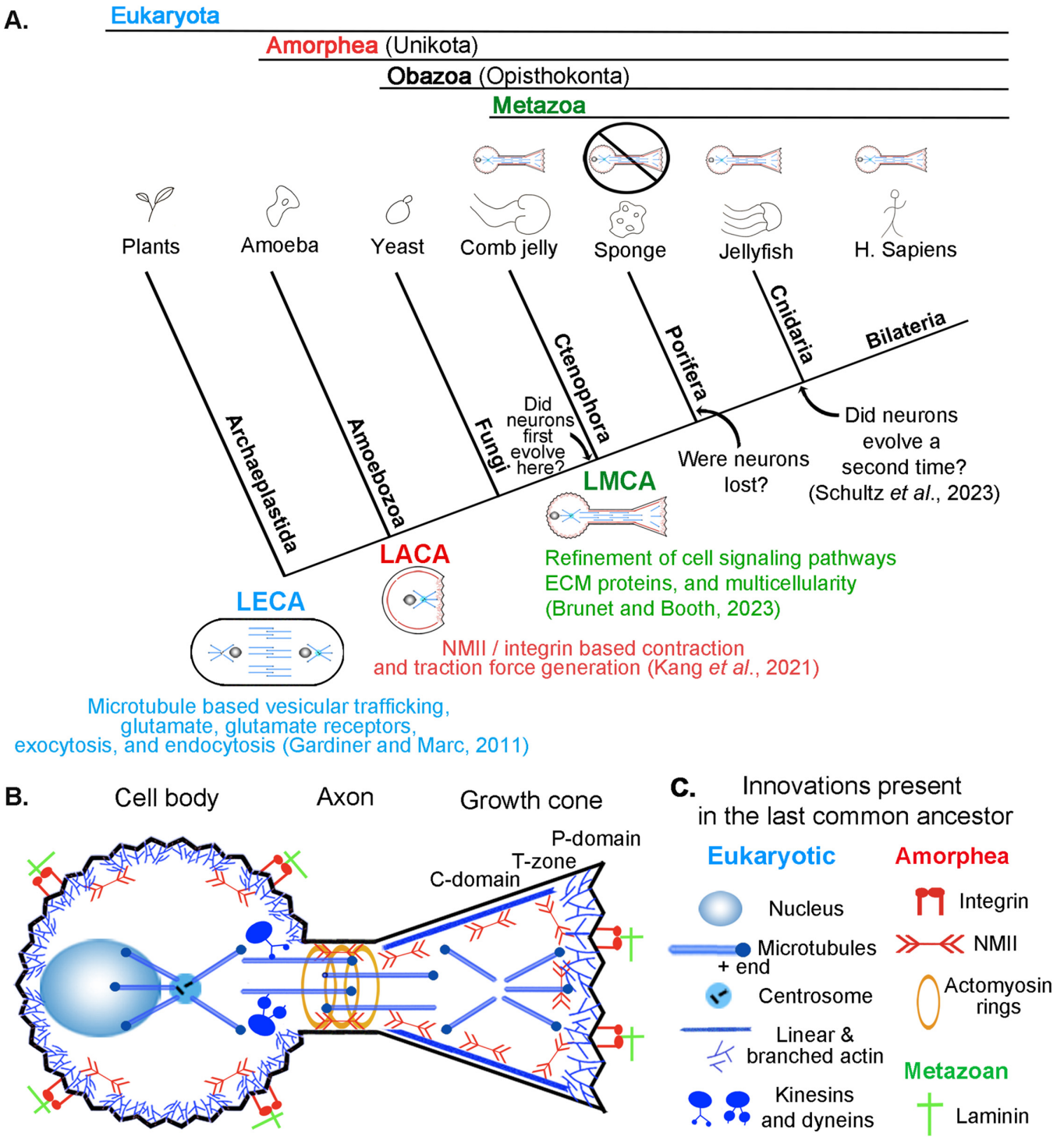

FIGURE 1: Core features of neurons date back to the LECA and the LACA and were used for cytokinesis. (A) Cladogram showing key events and the evolutionary origin of cytoskeletal features in neurons. Machinery used for synaptic transmission, powered cytokinesis in the LECA. Cell adhesion molecules and actomyosin-based contraction, which control axonal elongation, arose before Amoebozoa and may have assisted cell division or crawling in the LACA. The lack of neurons in sponges raises the question of whether neurons evolved once in the common ancestor to all metazoans and were subsequently lost in some lineages or evolved multiple times. (B) Color-coded schematic showing the evolutionary origin of the neuronal cytoskeleton. Machinery inherited from the LECA is labeled in blue. Innovations from the LACA, essential for traction force generation, including integrins and NMII, are shown in red. Laminin, an LMCA innovation, is shown in light green.

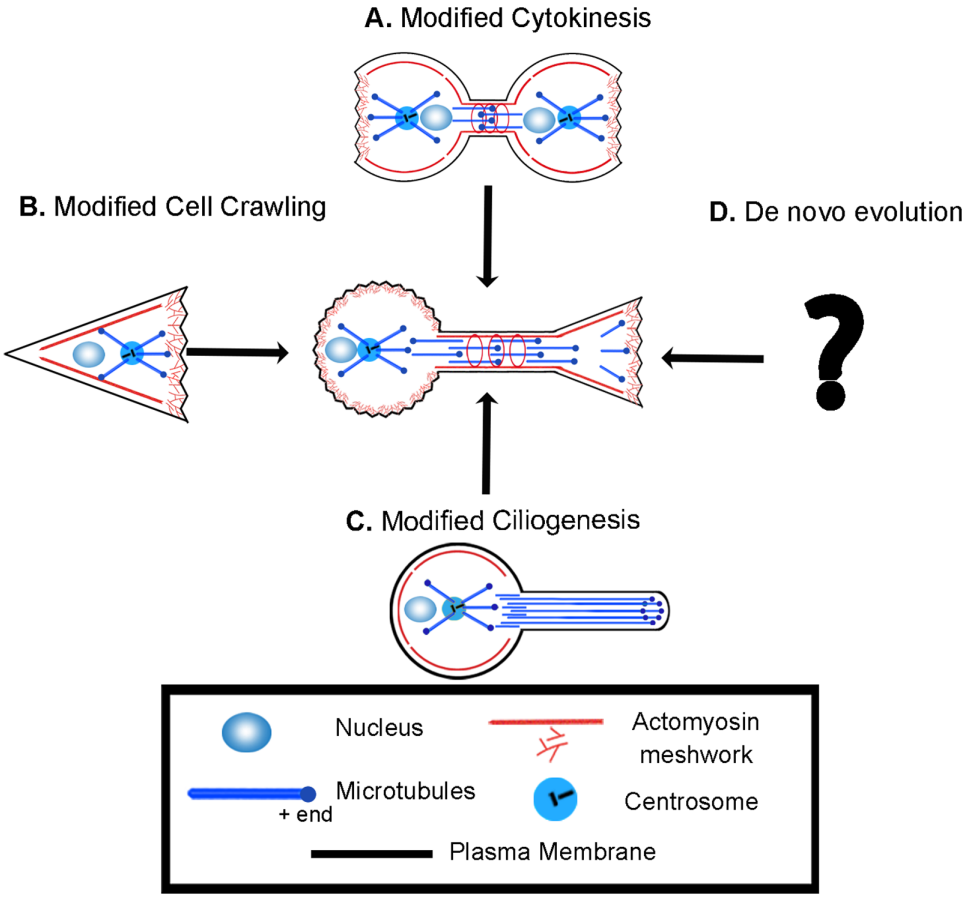

FIGURE 2: Four potential evolutionary paths to neurons. (A) Modified cytokinesis: the growth cone is homologous to the polar regions of dividing cells, and the axon to the cytokinetic bridge. (B) Modified cell crawling: the growth cone is homologous to a crawling cell, which forms a simple axon as it pulls away from the cell body. (C) Modified ciliogenesis: the axon is homologous to cilia; the growth cone is acquired later. (D) De novo evolution: the axon and the growth cone are novel evolutionary innovations unrelated to these other processes.

Because it existed before the evolution of nonmuscle myosin II (NMII) and integrins (Sebe-Pedros *et al.*, 2014; Kang *et al.*, 2021), which pinch and pull animal cells apart during division, it may have undergone cytokinesis using a mechanism similar to modern plants called cell plate formation (Muller and Jurgens, 2016; Yagisawa *et al.*, 2020; Sinclair *et al.*, 2022). This involves building a new cell plate through polarized secretion using microtubule-based delivery of vesicles mediated by SNARES, Syntaxin, CLASP, kinesin-12, and katanin (Livanos and Muller, 2019). Noting that these proteins are essential for both neuronal function and cytokinesis across eukaryotes suggests that axonal elongation may have evolved by repurposing ancient machinery that was initially used for cell division.

To further explore this problem, we next considered the evolutionary origin of the cytoskeletal machinery needed for axonal elongation, which is color-coded in Figure 1. Although the LECA-lacked proteins typically associated with contractile force generation and adhesion (i.e., NMII and integrins), it expressed sophisticated machinery for controlling the actin cytoskeleton, including profilin, Rac, WASP, and SCAR (Fritz-Laylin *et al.*, 2017; Pandey and Chaudhary, 2017). In addition, it is thought to have expressed the full array of dynein classes (axonemal, intraflagellar transport (IFT), and cytoplasmic dynein) (Kollmar, 2016), and most kinesin classes (i.e., Kinesin-1, 2, 3, 4/10, 5, 8, 9A, 9B, 13, 14, 17) (Wickstead *et al.*, 2010). These include Kinesin-5, which drives microtubule bundling and sliding, Kinesin-13, which modulates microtubule dynamics, and Kinesins 1, 2, and 3, which mediate intracellular transport (Joseph *et al.*, 2021). Collectively, these proteins are essential for endo- and exocytosis, vesicular trafficking, slow/fast axonal transport, axonal elongation, and synaptic function in modern neurons.

Noting that both plants and animals utilize glutamate and ionotropic glutamate receptors for cell–cell communication (Gardiner and Marc, 2011; Qiu *et al.*, 2019), current data suggest the LECA possessed essential components needed for synaptic transmission, growth cone lamellipodial formation, vesicular trafficking, and ESCRT-III-mediated axonal pruning and used these to power cytokinesis (Figure 1B). Of note, although plants appear not to form neuron-like synapses (Robinson and Draguhn, 2021), the extent of genetic overlap between the genes that drive plant cell division and neuronal function has led to the proposal that Arabidopsis may be an excellent model system to study the neuronal microtubule-based cytoskeleton (Gardiner and Marc, 2011). This suggests that neurons utilize ancient microtubule-based molecular mechanisms present in the last common ancestor of eukaryotic cells for their functioning. Because ciliogenesis and cell division were core features of the LECA, both start as reasonable candidates for being coopted during the evolution of neurons as a cell type.

Machinery for traction force generation in the LACA was used for cytokinesis and cell crawling

The next set of molecular innovations necessary for the evolution of neurons, metazoan cytokinesis, and cell crawling (i.e., amoeboid and mesenchymal migration) arose after the split between the lineages leading to plants and Amorphea (including animals) (Burki *et al.*, 2020) (Figure 1B). These involved the de novo evolution of NMII (Richards and Cavalier-Smith, 2005), which allowed cells to generate contractile forces on actin arrays and later integrins (Sebe-Pedros *et al.*, 2010; Kang *et al.*, 2021). Although the original purpose of both proteins has yet to be discovered, in modern cells, they are used to apply forces to substrates, which promotes cell crawling and the separation of daughter cells during cytokinesis. Alongside the evolution of force-sensing and regulatory proteins that link integrins to actin (e.g., talin, paxillin, and protovinculin/a-catenin), these innovations allowed cells to develop new approaches for cytokinesis and motility (Wang *et al.*, 2021; Brunet and Booth, 2023).

Later in the evolution of Eukaryotes, cells refined the process of secreting extracellular matrix molecules to assist with traction force generation. Initially, proteins with EGF/laminin and fibronectin III domains evolved into modern bilaterian ECM proteins such as laminin (Eichinger *et al.*, 2005). To better control subcellular gradients in force generation and adhesion, the cell polarity gene Par1/MARK also evolved during this period (Brunet and Booth, 2023). This complemented the activities of Rho family GTPases by directing the polarized secretion of extracellular matrix proteins and targeting the subcellular localization of mRNA. Between the last amorphea common ancestor (LACA) and the emergence of metazoans, genes essential for cell adhesion (e.g., classical cadherins, c-Src, FAK, and Cdc42) also evolved (Fort, 2017; Brunet and Booth, 2023). The coupling of cell-generated extracellular matrix with sophisticated machinery for generating and sensing forces in the Last Metazoan Common Ancestor (LMCA) provided the core physical and regulatory elements necessary for axon outgrowth (Craig *et al.*, 2024). Taken together, the early evolutionary history of eukaryotic cells suggests that many of the proteins required for axon outgrowth and synaptic transmission initially evolved to support cytokinesis and cell crawling (Figure 1). To evaluate which cellular processes have the closest relationships, we next consider the similarities and differences between the biophysics and molecular pathways that mediate cytokinesis, cell crawling, ciliogenesis, and axonal elongation.

Cytokinesis, cell crawling, and axonal elongation utilize similar physical mechanisms

Traits are heritable features that vary between individuals and affect fitness. Although often thought of in terms of morphological features, such as limb shape, features of metabolic processes like glycolysis and rates of cell growth are also traits (Caetano-Anolles *et al.*, 2009). Thus, when considering whether two morphological structures are evolutionarily related, their shapes and the underlying processes that form them are useful for evaluating relationships. In particular, when two similar structures form through convergent evolution, the underlying processes that form them can be radically different (Stern, 2013). An excellent example is the flagella of bacteria and eukaryotic cells, which are outwardly similar but internally constructed using different molecules (Khan and Scholey, 2018). In turn, morphologically distinct structures, such as human hands and bat wings, are evolutionarily related (i.e., homologous) because the genes and mechanisms of formation have a shared origin (Cooper *et al.*, 2012). In this next section, we use cytoskeletal flow maps as a trait to better understand the evolutionary relationships between axonal elongation, neuronal migration, cell crawling, and cytokinesis.

Though the morphology of neurons differs dramatically from that of nonneuronal cells, examination of underlying cytoskeletal flow patterns suggests that cytokinesis, cell crawling, and axonal elongation may be closely related (Craig *et al.*, 2024) (Figure 3). Although the classic view was that axons elongate through the assembly of materials at the tip of stationary microtubule framework (Bamburg *et al.*, 1986), modern studies using time-lapse microscopy reveal that, like crawling cells, the cytoskeletal elements in axons (Miller and Suter, 2018; Burute *et al.*, 2022), and the leading process of migrating neurons (Guan *et al.*, 2007; He *et al.*, 2010; Hutchins and Wray, 2014; Minegishi *et al.*, 2018) flow in bulk (Figure 3, D and E). Here, it is interesting to note that while microtubules flow toward the cell body during the initial outgrowth of cortical/hippocampal neurons, this switches to forward flow as the neurites mature into axons (Burute *et al.*, 2022; Schelski and Bradke, 2022). In other neuronal cell types and bilaterians, including *Aplysia* bag cell neurons, *Drosophila* motor neurons, *Xenopus* spinal cord neurons, and chick and rat peripheral neurons, microtubules flow toward the growth cone during elongation (Reinsch *et al.*, 1991; Miller and Sheetz, 2006; Lamoureux *et al.*, 2010; Roossien *et al.*, 2013; Athamneh *et al.*, 2017).

In turn, consistent with the idea that cytokinesis and cell crawling are closely related processes, it has long been appreciated that cortical flow patterns established during cytokinesis continue into interphase and power cell motility (Swann and Mitchison, 1958; Bray and White, 1988; DeBiasio *et al.*, 1996). During cytokinesis, Rho activation establishes the site of the cleavage furrow (Pollard and O'Shaughnessy, 2019). This activates NMII, which drives symmetrical inward cortical flow, which is evident in the kymograph and velocity profile from a figure adapted from (Craig *et al.*, 2024) (Figure 3A). Simultaneously, Rap activation under the polar regions of dividing cells turns on integrins, generating inward-pointing traction forces (Dix *et al.*, 2018; Taneja *et al.*, 2019), while gradients in Ran modulate microtubule dynamics and motors (Ozugergin and Piekny, 2021). Immediately following cytokinesis, the cytokinetic bridge becomes the trailing edge of the two daughter cells, and the polar regions transition into the leading edges, producing cellular motion (Figure 3, B and C). The subcellular velocity profiles of cytokinesis, amoeboid migration, and mesenchymal migration are all similar in that they have a primary convergence zone into which materials flow (Figure 3, A and C). They differ in that during cell migration, the zone of high Rho activity and, thus, contractile activity expands. Also, instead of being symmetrical, crawling cells typically have a single region with high cell adhesion downstream of Rap. Thus, the biophysics and the subcellular patterns of Rho, Rap, Rac, and Ran activation suggest that crawling cells physically behave like half of a dividing cell.

In turn, amoeboid and mesenchymal migration resemble neuronal migration in that, as the cells move forward, the underlying cytoskeleton advances, as seen by comparing the kymographs and subcellular velocity profiles (Figure 3, B–D). Where they differ is that the zone of contractile activity that drives leading-edge retrograde actin flow extends over large regions of crawling cells but is restricted to a narrow region in growth cones. Thus, the overall shapes of the flow and traction force maps are qualitatively similar in cell crawling and neuronal migration. Likewise, when focusing on the distal axon, the process of axonal elongation resembles neuronal migration. In both, a convergence zone in the growth cone

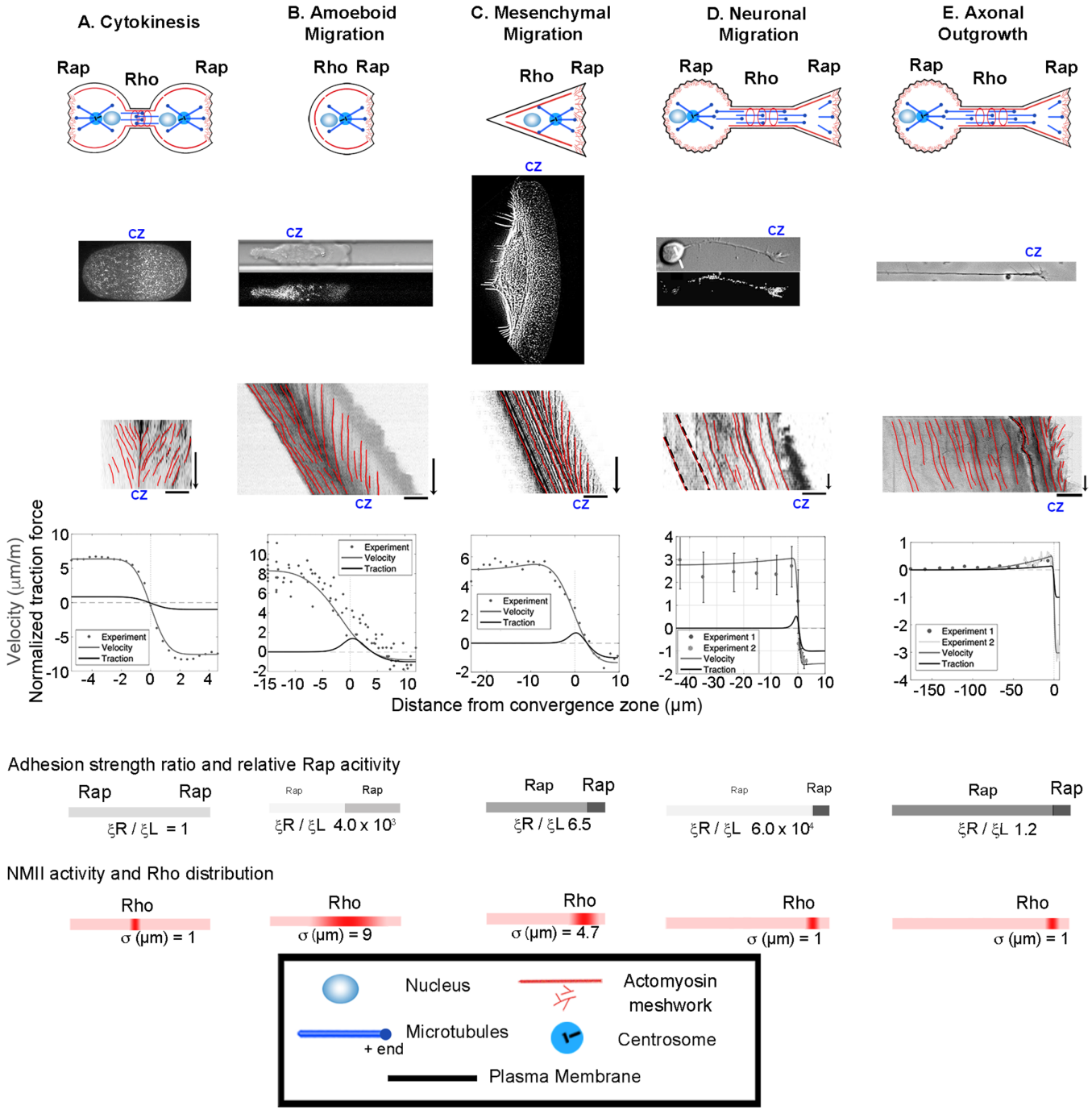

FIGURE 3: Cytokinesis, cell crawling, and axonal elongation utilize shared biophysical mechanisms. Each panel shows a schematic, a still image, a kymograph, a velocity profile, and a normalized traction force profile for a cellular process. Maps of adhesion, motor activity, and Rho GTPase activities are shown at the bottom. (A) During cytokinesis, Rho induces a convergence zone, which drives the inward flow. Because adhesions are symmetric, traction forces are balanced, and cells are stationary. (B) Cells undergoing amoeboid migration resemble a dividing cell with only adhesions on one side. (C) The transition to mesenchymal migration involves globally increased cell adhesion and a shift of the convergence zone toward the leading edge. (D) During neuronal migration, the leading process advances in tandem with the cell body. The convergence zone and rapid lamellipodial retrograde actin flow are restricted to the growth cone. (E) Axonal elongation resembles neuronal migration over the distal region of the axon. The major difference is that high levels of adhesion under the axon and cell body cause velocity to decrease away from the growth cone, and the cell body to remain stationary. Adapted with permission from (Craig *et al.*, 2024).

drives retrograde actin flow, while microtubules and associated organelles in the axon/leading process flow forward in bulk (Figure 3, D and E). The primary difference between migration and elongation is that, during elongation, the strength of adhesions under the cell body is high, which causes it to remain stationary. Collectively, this suggests that cytokinesis, amoeboid migration, mesenchymal migration, neuronal migration, and axonal elongation may be related. In each, a primary contractile zone, organized by Rho, drives inward flow, while differences in patterns of subcellular adhesion, modulated by Rap and Rac, control traction force generation and motion. Thus, at the physical level, axonal elongation appears to be a variation of the same process that drives cytokinesis and different modes of cell crawling.

In contrast, although axons and cilia appear outwardly similar, ciliogenesis uses a different physical mechanism, which involves microtubule assembly at the tip of a stationary array of microtubules controlled by IFT (Patra *et al.*, 2020). And, unlike the microtubules extending into axons, these microtubules are linked to the cell body via the basal body, and their assembly is controlled through cilia-specific proteins (Avasthi and Marshall, 2012). Although microtubule sliding is a robust feature of cilia, it powers their rhythmic motion instead of elongation. In short, the mechanical process of axonal elongation more closely resembles cytokinesis and cell migration than ciliogenesis. This suggests that the outwardly similar morphology of cilia and axons may result from convergent evolution rather than homology. Nonetheless, it is important to note that there is extensive overlap and connections between the genes that drive ciliogenesis and cytokinesis (Ou and Scholey, 2022). This suggests the need for establishing the evolutionary relationships between cytokinesis, ciliogenesis, mesenchymal migration, amoeboid migration, neuronal migration, and axonal elongation.

Rho, Ran, and Rap signal transduction pathways control force generation and adhesion

Cellular physical processes occur through well-studied modules of Rho family GTPases, which activate evolutionarily conserved effector proteins to control force generation and cell adhesion (Beljan *et al.*, 2020). Before discussing the molecular similarities and differences between processes, we will briefly review these modules to bridge the gap between cellular biophysics and molecular pathways.

Broadly, Rho acts to create actomyosin-based convergence zones into which materials flow (Filic *et al.*, 2021). It does so by activating formin and ROCK, which induce unbranched actin assembly and NMII-based contraction (Figure 4A). Complementing this, Ran GTPase modulates microtubule assembly, microtubule bundling, and microtubule motors to generate forces that can be contractile or extensile (Chen *et al.*, 2017; Ozugergin and Piekny, 2021). Meanwhile, Rap is a master organizer of cell adhesion and, thus, traction force generation. It signals through GEFs and GAPs to activate Rac and talin, creating branched actin meshworks linked to the substrate through cell adhesion molecules, including cadherins and integrins (Shah and Puschel, 2016; Jaskiewicz *et al.*, 2018).

Together, patterns of Rap, Rho, and Ran activity at the leading edge of crawling cells, growth cones, and the polar regions of dividing cells organize traction force machinery. High levels of Rap induce substrate attachment, a localized region of Rho activity induces NMII contraction powering flow, and high levels of Ran activity at the leading edge of crawling cells and in growth cones activate dynamic microtubules (Figure 4B). In turn, at the cleavage furrow of dividing cells and along axons, high levels of Rho activity induce NMII activity, tension, inward flow, and circumferential constriction. Paired with this, molecular motors and microtubule-associated proteins bundle and slide microtubules to generate forces. As a result of the combined activity of the actin and microtubule cytoskeleton, cytokinetic bridges and axons are formed (Figure 4C). With this background, we next focus on the molecular parallels and differences in these pathways to evaluate the relationship between cytokinesis and axonal elongation.

Signaling pathways that regulate cytokinesis control axonal elongation

Although neurons are notable for not dividing, many cell-cycle genes modulate neuronal morphology and synaptic functioning. For example, as reviewed in Frank and Tsai (2009), the ubiquitin ligase APC, which acts on Cdh1 and Cdc20, modulates axonal growth, dendrite morphogenesis, and synapse formation. Cohesion, which links chromatids, is involved in axon pruning and dendritic targeting. Whereas Aurora A kinase, Polo-like kinase 2, and CDK5 modulate synaptic strength. In turn, in Alzheimer's disease, neurons misexpress mitotic genes, including CDK1, CDK4, CDK5, cyclin A, cyclin D, cyclin E, $p16^{INK4a}$, and $p27^{Kip1}$. This causes neurons to dedifferentiate and reenter the cell cycle (Arendt, 2003). These observations suggest a close link between the genes that control division and neuronal function.

To consider the parallels and differences between cytokinesis and axonal elongation, we next compare the cell signaling pathways and effector proteins that drive these processes. For an excellent review of the Rho signaling axis in the context of cell division, see Pollard and O'Shaughnessy (2019). Reviews for Rap and the link with Rac are provided in the following reference (Arthur *et al.*, 2004; Frische and Zwartkruis, 2010; Gloerich and Bos, 2011; Shah and Puschel, 2016). The Ran GTPase pathway is summarized in Ozugergin and Piekny (2021). To illustrate, we show key proteins in these pathways, their interactions, and downstream effectors linked together (Figure 5A). In both the signaling and cellular diagrams, the Ran pathway and its subcellular pattern of activation are shown in green, while Rho and Rap are color-coded blue and red, respectively (Figure 5C).

During cell division, as interphase animal cells enter mitosis, Ran activates Aurora A Kinase, which promotes centrosome maturation and mitotic spindle assembly (Willems *et al.*, 2018). Due to its interaction with Aurora A Kinase, TPX2 induces microtubule nucleation by activating γ-Tubulin ring complexes. Microtubule assembly is further modulated by microtubule end-binding proteins, including EB1, CLASP, and CAMSAP/Patronin (Akhmanova and Steinmetz, 2015; Yamada and Goshima, 2017). During this process, cells partially detach from the substrate and round. The loss of adhesions occurs due to a global downregulation of Rap, which normally acts to promote Rac and integrin activation during interphase (Dao *et al.*, 2009). Additionally, the export of the RhoGEF Ect2 from the nucleus at prophase causes global activation of Rho at the cell cortex, isotropic NMII activation, formin-mediated actin assembly, and downregulation of Rac/Cdc42-controlled cell adhesions (Rosa *et al.*, 2015; Dix *et al.*, 2018; Pollard and O'Shaughnessy, 2019). Because NMII is initially isotopically activated, cortex tension rises, which drives rounding, but the flow rate remains low. At metaphase, this results in cells that are roughly spherical and loosely attached to the substrate, with two mitotic spindles consisting of astral, kinetochore, and polar (nonkinetochore) microtubules (Prosser and Pelletier, 2017).

After chromosome capture and passage through the spindle checkpoint, anaphase begins. Three primary force-generating

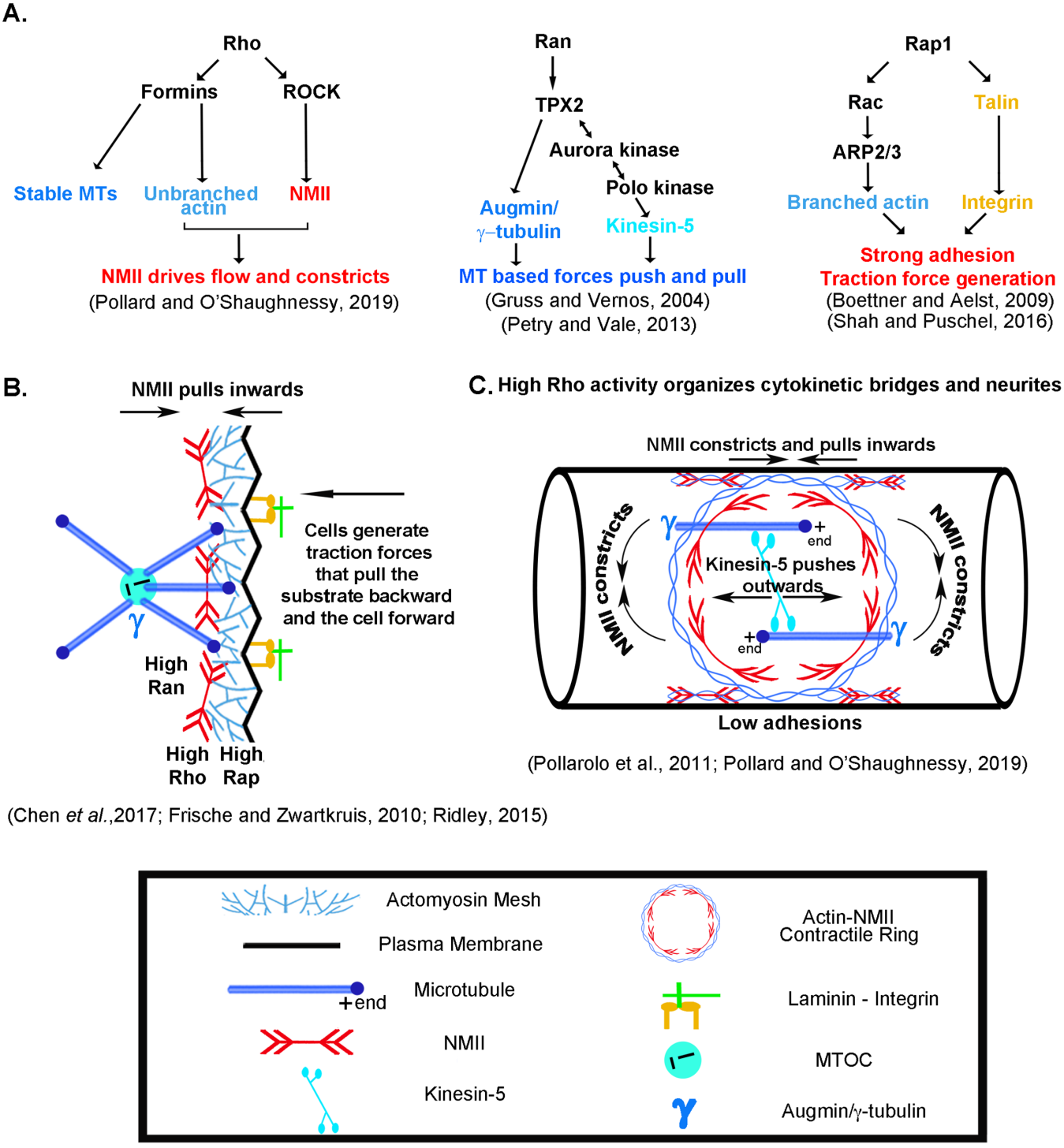

FIGURE 4: Rho, Ran, and Rap signaling pathways control microtubule and actin dynamics during cytokinesis, cell crawling, and axon outgrowth. (A) Key effectors and cellular activities for each pathway. (B) Diagram showing cytoskeletal mechanics found under the polar region of dividing cells, at the leading edge of crawling cells, and growth cones. (C) Illustration of features found in cytokinetic bridges and neurites.

mechanisms then work to divide the cell: Rho-mediated circumferential actomyosin constriction at the midline, which pinches the cell in two to form the cytokinetic bridge; Ran-mediated microtubule-based extensile forces that push cells apart; and Rap actin-based traction forces that pull the nascent daughter cells apart (Figures 4, B and C and 5C). Coordinating this, centralspindlin, a complex of Kinesin-6 and MgcRacGAP, bundles microtubules and locally stimulates Ect2, which activates Rho at the midline to create a contractile zone (Pollard and O'Shaughnessy, 2019) (Figure 5A). Rho and its effectors activate formin to generate linear arrays of actin and NMII to drive flow, while NMII and cofilin disassemble the actin meshwork to prevent accumulation at the cleavage furrow.

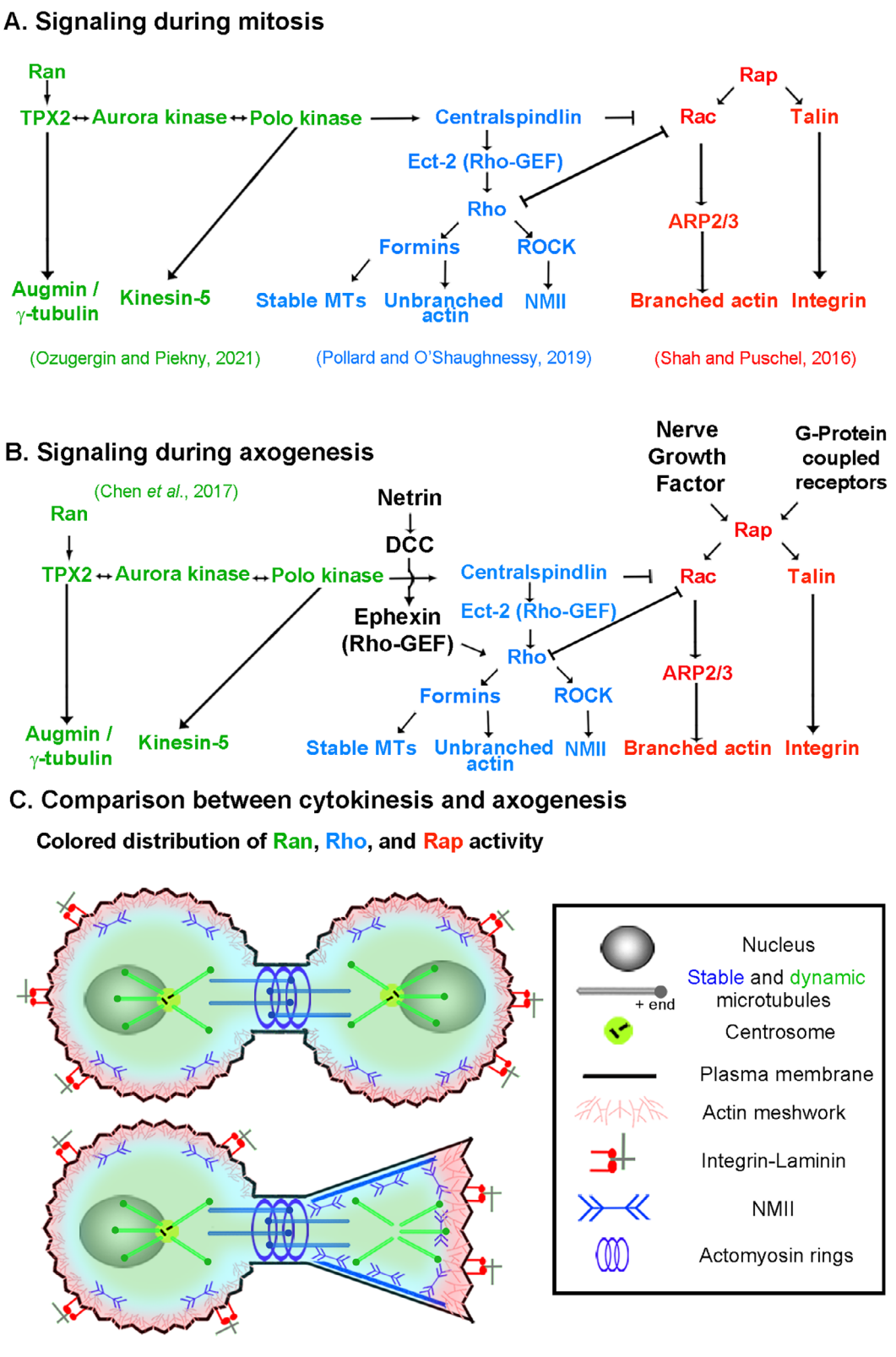

FIGURE 5: Cytokinesis and axogenesis utilize shared signaling pathways. (A) Overview of key molecular components mediating cytokinesis. (B) Axonal elongation differs at the upper levels, noted by molecules labeled in black. (C) Color-coded schematic of a dividing cell and neuron. Ran and Rap activities are elevated at the leading edge of growth cones and under the poles of dividing cells, shown in green and red. Rho activity, illustrated in blue, is high at the cleavage furrow, in the growth cone transition zone, and along axons. In neurons, a periodic arrangement of actin rings and spectrin stabilizes axons (Xu *et al.*, 2013; Dubey *et al.*, 2020). During cytokinesis, spectrin stabilizes actomyosin rings, which contract to form the cytokinetic bridge (Sobral *et al.*, 2021).

During this process, plastin and spectrin cooperate to stabilize actin around the cytokinetic bridge (Sobral *et al.*, 2021). Collectively, this generates a circumferential band of elevated contraction and, thus, constriction and flow toward the midline (Singh *et al.*, 2019). Simultaneously, high levels of Rap and, thus, Rac activity occur toward the poles, activating WASP, ARP2/3, NMII, and integrins (Jordan and Canman, 2012). This results in traction force generation that pulls the two daughter cells apart (Taneja *et al.*, 2019) (Figure 4B). Complementing this, Kinesin-5 bundles microtubules and generates extensile forces that push antipolar microtubules apart (Cross and McAinsh, 2014) (Figure 4C). Collectively, the combination of contraction at the midline, traction forces at the poles, and microtubule extensile forces push and pull to form two daughter cells connected by a cytokinetic bridge (Figure 5C). Cell division is then completed by the process of abscission via the ESCRT-III complex, which cleaves the cytokinetic bridge (Andrade and Echard, 2022). To assess the similarities and differences between cell division and axonal elongation, we next discuss this same pathway in the context of axon outgrowth.

Genes involved in animal cell cytokinesis and axon outgrowth overlap

Like with cytokinesis, the Rho family GTPases, Ran, Rho, and Rap, orchestrate all phases of neuronal development. This includes axonal initiation, elongation, and guidance (Hall and Lalli, 2010) (Figure 5B). Rap, which controls adhesion under the poles of dividing cells, is activated by NGF and cAMP in neuronal growth cones (Figure 5C) and regulates cadherin and integrin-based adhesions during neocortical development and synaptic plasticity in adults (Shah and Puschel, 2016). In turn, Rho signaling, which is central to cytokinesis, is a promising target for neuronal regeneration. In neurons, Rho is regulated in part by the centralspindlin complex (i.e., Kinesin-6 and MgcRacGAP), which modulates axonal elongation (Falnikar *et al.*, 2013). In accordance, disruption of the RhoGEF Ect2, which links centralspindlin and Rho, impairs axonal guidance and synaptogenesis (Koizumi *et al.*, 2007) and increases growth cone number (Tsuji *et al.*, 2012). Similar to Rap, specialized proteins have evolved, for example, the Netrin–DCC pathway, allowing extracellular guidance cues to control Rho signaling and thus axonal elongation. Likewise, Ran, which is the primary regulator of the microtubule cytoskeleton during cytokinesis, controls microtubules in neurons to promote axon outgrowth (Chen *et al.*, 2017) (Figure 5C). Its downstream effector, Aurora A kinase, in tandem with atypical protein kinase C (aPKC) and NDEL1, acts at the axon hillock to organize microtubules and to promote axon initiation and elongation (Mori *et al.*, 2009; Pollarolo *et al.*, 2011; Blazejewski *et al.*, 2021). As a result of TPX2 activation, γ-Tubulin, alone and assisted by Augmin, helps establish microtubule polarity in axons and dendrites (Nguyen *et al.*, 2014; Sanchez-Huertas *et al.*, 2016). As a result of these activities, Dynein and Kinesin-5 generate forces that control neuronal microtubule sliding and outgrowth (Myers and Baas, 2007; Roossien *et al.*, 2014). Thus, the signaling pathways that control cell division control axonal elongation.

Downstream of these signaling pathways, the cytokinesis effector proteins Wasp/Scar, Arp2/3, formin, profilin, and cofilin have all been shown to be critical for elongation and growth cone guidance (Wills *et al.*, 1999; Kuhn *et al.*, 2000; Arakawa *et al.*, 2003; Strasser *et al.*, 2004; Shekarabi *et al.*, 2005). Likewise, NMII and integrins, which generate forces and traction during cell division, control elongation and cell adhesion in neurons (Condic and Letourneau, 1997; Bridgman *et al.*, 2001; Wylie and Chantler, 2001). Additionally, septins and anillin, proteins that mark the site of cytokinesis initiation and organize cell signaling, are also essential for axon initiation, axo-dendritic sorting, axon outgrowth, synapse formation, axon branching, and neuronal migration (Tian *et al.*, 2015; Falk *et al.*, 2019; Radler *et al.*, 2023). Finally, the ESCRT-III complex, which cleaves the cytokinetic bridge during abscission (Lafaurie-Janvore *et al.*, 2013; Andrade and Echard, 2022), prunes unneeded axon branches during development (Loncle *et al.*, 2015). Collectively, this suggests that signaling pathways and cytoskeletal effectors that control cytokinesis play analogous roles in axonal elongation.

Are axons modified cilia?

Cilia and flagella are ubiquitous structures that protrude from nearly all human cells, including neurons (Satir and Christensen, 2007). Although highly similar, flagella and cilia differ in form and function: cilia tend to be numerous, short, and are often involved in sensory function, whereas flagella tend to be long and often drive cell locomotion. The idea that axonal elongation evolved from the mechanisms used to create cilia and flagella is appealing because these structures are all constructed from bundled microtubules. Like axons, their outgrowth requires robust microtubule-based transport, microtubule assembly, and is tightly coordinated with the cell cycle (Avasthi and Marshall, 2012). Nonetheless, unlike axons, the microtubule-based structure inside cilia and flagella, called the axoneme, extends from a basal body (Carvalho-Santos *et al.*, 2011). In turn, Although axons typically have singlet microtubules cross-linked with MAPs such as tau and MAP2 (Sundermann *et al.*, 2016), axonemes are characterized by having nine doublet microtubules, which surround two singlet microtubules in motile cilia, with a basal body at the base (Satir and Christensen, 2007). These microtubules are cross-linked by a nexin-dynein regulatory complex and utilize axonemal dynein, which is absent in axons, to drive motion (Heuser *et al.*, 2009). Finally, axonemes lack a cortical actin meshwork (Hoffman and Prekeris, 2022). Thus, there are significant differences in the cytoskeletal organization of axonemes and axons.

Additionally, the transport processes that underlie ciliogenesis and axonal elongation differ dramatically. The length of cilia is tightly regulated by IFT machinery, which uses Kinesin-2 to move cargoes out of the cell body (IFT-B) and a specialized cytoplasmic dynein-2 for retrograde transport (IFT-A) (Roberts, 2018). Although Kinesin-2 supports axonal transport in neurons (Ray *et al.*, 1999), cytoplasmic dynein-2 has no known role in axonal transport. Furthermore, unlike axons, IFT cargos lack membranes, and other membrane-bound cargoes such as mitochondria and endosomes are absent. In terms of elongation, ciliogenesis occurs as the result of microtubule assembly at the tip, which is regulated by the cilia-specific proteins FAP256/CEP104, CHE12/Crescerin, and ARMC9 (Louka *et al.*, 2018; Reynolds *et al.*, 2018), which make up the flagellar tip complex.

Although these differences do not exclude the possibility of axon outgrowth evolving directly through the modification of ciliogenesis, an evolutionary pathway linking them would involve a substantial loss and gain of molecular components. These include a loss of connection between the basal body and axonal microtubules, the loss of the characteristic 9 + 2 arrangement of microtubules, a significant loss of cilia-specific genes involved in modulating ciliogenesis and generating flagellar motion, the loss of IFT-specific machinery, and the gain of genes essential for growth cone-mediated substrate adhesion and the axonal transport of membrane-bound organelles. These observations suggest that if axonal elongation evolved from ciliogenesis, the process involved major modifications in cytoskeletal composition and organization.

Hypothetical pathway for the evolution of axons

The essential role of the axon as a structure is to transmit information and molecules over long distances while minimizing the energetic costs associated with maintaining cellular function. As such, the morphology of a long, thin cylinder with robust transport mechanisms is an excellent solution. Although similarities between cytokinesis, cell crawling, and axon formation suggest extensive repurposing of cellular machinery, the formation of the first axon must have involved a novel molecular event.

Using metazoan cellular development as a framework to discuss neuronal evolution, after DNA replication and centriole duplication, cells in the G_2 phase of the cell cycle enter mitosis (Pollard and O'Shaughnessy, 2019) (Figure 6A). The coordinated activation of Ran, Rho, and Rap generates an antiparallel array of microtubules that forms the cytokinetic bridge, actomyosin contraction that pinches the cell in two, and the activation of polar traction force machinery that pulls daughter cells apart (Figure 6B). Cell crawling can occur immediately after the bridge is cleaved by abscission, through the partial continuation of mechanisms initiated during mitosis (Bray and White, 1988; DeBiasio *et al.*, 1996) (Figure 6C). Likewise, for cells fated to become neurons, axon initiation occurs minutes after the completion of cytokinesis during G1 phase (Pollarolo *et al.*, 2011). It is also organized by the mitotic signaling proteins Aurora A kinase and Rho and requires the formation of an antiparallel microtubule array (del Castillo *et al.*, 2015) (Figure 6D). Coupled with the activation of traction force generation by the actin cytoskeleton, the growth cone forms, and pulls away (Figure 6E).

Here, it is interesting to note that the establishment of an antiparallel microtubule array (Figure 6D), like that found in the mitotic spindle, has been suggested to be essential for neurite initiation (del Castillo *et al.*, 2015). The observation that dendrites in some modern bilaterians contain microtubule organizing centers (MTOCs) and antiparallel microtubules (Wilkes and Moore, 2020) raise the question of whether the first neuronal extensions inherited their microtubule organization from the mechanism used to create the mitotic spindle (Figure 6D). If this model is correct, it suggests that the mixed organization of microtubules in dendrites may be ancestral, and the parallel arrays of microtubules in modern axons are a more recent innovation. In turn, the repurposing of the cytokinetic actomyosin cytoskeleton, which is stabilized by spectrin and plastin, provides a plausible evolutionary pathway leading to the periodic meshwork of spectrin and actin in mature axons (Xu *et al.*, 2013; Dubey *et al.*, 2020; Sobral *et al.*, 2021).

As to the potential molecular mechanism initiating axon evolution, we note that the most significant differences between cytokinesis and axonal elongation occur at the upper levels of their signal transduction pathways (compare Figure 5, A and B). This suggests the hypothesis that mutations at this level partially activated cytokinesis during interphase before DNA replication (Figure 6D). As a result, the side of the cytokinetic bridge containing the nucleus became the neuronal cell body, while the other side became the growth cone (Dao *et al.*, 2009; Taneja *et al.*, 2019) (Figure 6E). Yet, instead of abscission ensuing immediately, activation of the ESCRT-III complex is delayed and used later to prune neuronal extensions (Loncle *et al.*, 2015; Andrade and Echard, 2022).

As to what drove axon evolution, we speculate that there was selection pressure on a cell to bridge long distances while minimizing cell volume and resisting forces induced by body growth or motion. Repurposing the machinery used for cytokinesis may have solved three physical problems. It created a thin region that could be stretched as a result of sustained forces generated dur-

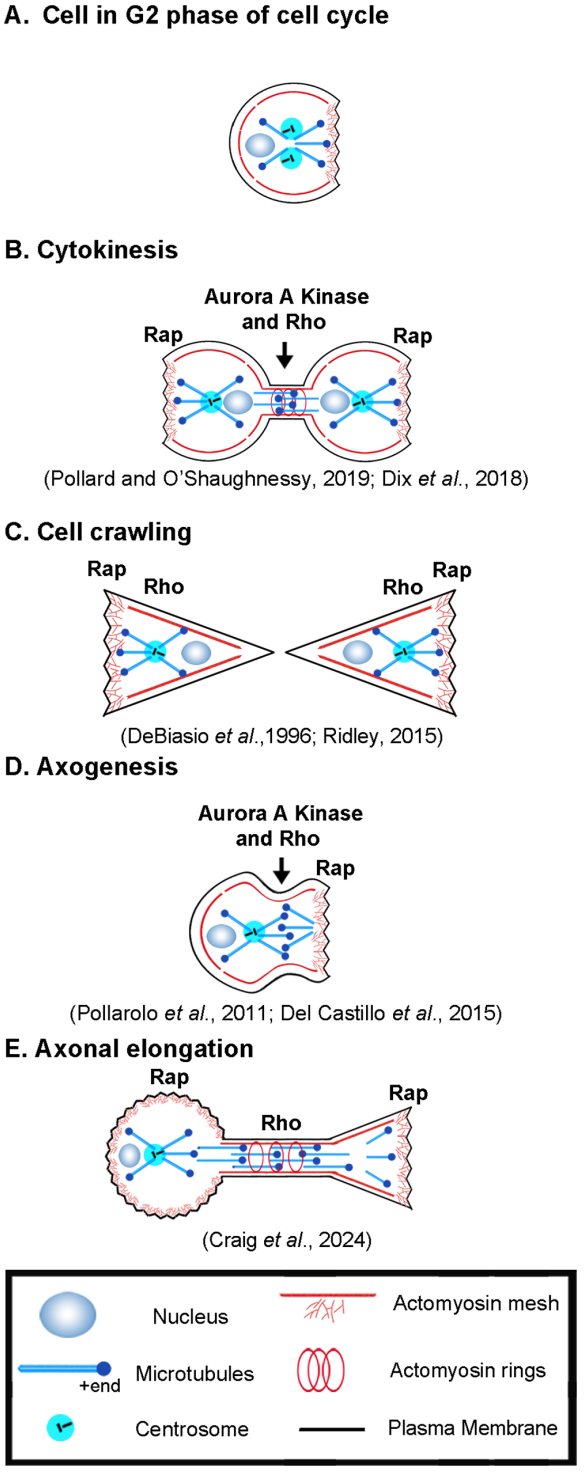

FIGURE 6: The Evo/Devo pathway of axon formation. (A) A modern metazoan cell with duplicated centrioles and DNA before mitosis. (B) Activation of Rho drives constriction, Aurora A kinase organizes microtubules, and Rap activates integrins, which pull dividing daughter cells apart. (C) Cell crawling occurs by using the traction force machinery that assists cytokinesis. It may have evolved as the result of continued activation during interphase. (D) Axon formation is induced by actomyosin constriction and microtubule reorganization through Rho and Aurora A kinase signaling. Axons may have evolved by partially activating cytokinesis during interphase. (E) Axonal elongation occurs as the growth cone crawls away from a stationary cell body, and microtubules reorganize.

ing axonal elongation; it minimized the volume and thus the resources needed to maintain neurons; and, it helped protect axons from forces associated with body motion by reusing the cortical meshwork of spectrin, plastin, actin, and myosin that maintains cellular integrity during cytokinesis (Wang *et al.*, 2008; Smith, 2009; Tofangchi *et al.*, 2016; Dubey *et al.*, 2020; Sobral *et al.*, 2021).

Did growth cones evolve from the machinery used to drive cytokinesis, cell crawling, or a combination of both?

Although the hypothesis that axonal elongation evolved as a modified form of cell crawling is only briefly discussed here, we initially favored it as an explanation based on the parallels between their biophysical and molecular mechanisms (Miller and Suter, 2018; Craig *et al.*, 2024). In brief, the hypothesis is that mutations in early metazoans locally activated traction force machinery, which pulled out a thin cytoplasmic process that later evolved into an axon. Over evolutionary time scales, the overlap between the genes involved in cytokinesis and axonal elongation is explained by the recruitment of cytokinetic proteins through convergent evolution (Stern, 2013). The strength of this model lies in its ability to explain the similarities between the morphology and mechanics of growth cones and crawling cells (Dogterom and Koenderink, 2019; SenGupta *et al.*, 2021). Its weakness is that it does not explain why many proteins involved in cytokinesis, such as septins and the ESCRT-III complex, play essential roles in neuronal function, such as controlling axonal branching and pruning (Loncle *et al.*, 2015; Falk *et al.*, 2019).

Although the available data are consistent with partial activation of cytokinesis as the origin of axons, the evolutionary origin of growth cones is less clear. Although growth cones may be homologous to polar traction force machinery, a more nuanced view is that growth cones evolved as the result of merging the signaling pathways that drive cytokinesis with the cytoskeletal effectors active during interphase that power cell crawling. In essence, a horizontal/lateral gene transfer event that merges the activity of gene modules normally separated by the timing of their expression, instead of from different species (Boto, 2010). This suggests the hypothesis that growth cones evolved by combining the regulatory mechanisms used for the induction of polar traction force generation during cytokinesis with the effector proteins present in interphase cells that mediate cell crawling.

DISCUSSION

Ways forward

In discussing the evolution of cellular mechanisms, we use the terms homology and convergent evolution, as molecular biologists, to indicate whether or not an evolutionary relationship exists (Patterson, 1988). By abstractly considering cellular processes as "species," each associated with the activities of subsets of genes within a genome, we ask how they are related based on the activity of genes required for each process. A challenge in understanding axonal elongation is that it utilizes genes essential for different cellular processes, in particular, cell crawling and cytokinesis. Although convergent evolution may explain this (Stern, 2013), the idea that two cellular processes within a cell can merge may be critical for understanding how a process as complex as axonal elongation seemingly evolved so abruptly and perhaps independently (Burkhardt, 2022).

Noting that cytokinesis, ciliogenesis, cell crawling, and axonal elongation all have unique aspects but are closely related, we suggest that developing an evolutionary tree linking cytokinesis, ciliogenesis, amoeboid migration, mesenchymal migration, neuronal migration, dendrite elongation, and axonal elongation (Craig *et al.*, 2024) is a needed long-term goal to understand how axons and dendrites evolved. As a starting point, gene ontology terms could be used to generate sets of genes associated with each process, followed by the creation of functional similarity trees (Koc and Caetano-Anolles, 2017). To infer phylogeny, this would need to be coupled with knowledge about when different cellular processes and essential genes first emerged. In doing so, careful consideration of cell type, cell state, gene networks, horizontal gene transfer, and the modularity of biochemical processes will likely be essential (Caetano-Anolles *et al.*, 2009; Boto, 2010; Arendt *et al.*, 2019).

To discover the molecular evolutionary events that gave rise to axons, a logical path forward will be to identify neuronal genes that are necessary and sufficient to induce the formation of axons. Toward this goal, a detailed phylogenetic analysis of the evolutionary history of metazoan axons and dendrites will lead to deeper insights. A current challenge is that while evidence is accumulating that suggests that *Ctenophores* (comb jellies), instead of *Porifera* (sponges), are the first lineage to diverge from the rest of animals (Schultz *et al.*, 2023), whether the cells called neurons in *Ctenophores* are homologous to bilaterian neurons or are the result of convergent evolution remain unknown (Burkhardt *et al.*, 2023) (Figure 1B). In particular, the lack of a neuronal-specific marker shared between *Ctenophores* and other *metazoans* leaves this an open question. Given the current state of knowledge, a critical step in understanding the evolution of neurons and axons will be determining whether *Ctenophore* and Bilaterian neurons share a common origin. If so, shared neuronal genes and structural features were likely present in the neurons of our last common ancestor and represent strong candidates for the novel innovation(s) that generated the first axon. In contrast, if neurons in *Ctenophores* and bilaterians reflect convergent, parallel, or collateral evolution (Stern, 2013), understanding how different evolutionary histories yield cell types with similar functions may provide novel insights into how to coax any given cell type into generating an axon-like process. Further triangulating this, if sponges are derived from a lineage that possessed neurons yet lost them (Ryan and Chiodin, 2015), the genes required for neuron formation should be mutated such that their function in inducing axon formation was lost. Likewise, given that choanoflagellates, single-celled protists, are currently thought to be the closest extant species before the split leading to metazoans, they arguably lack a subset of the molecular innovations needed to create neurons and will serve as a useful outgroup (Carr *et al.*, 2008).

In turn, a cell biological approach to complement phylogenetic analysis will be to start with lists of genes that are known to be required for cytokinesis (Glotzer, 2005; Eggert *et al.*, 2006), ciliogenesis (Avasthi and Marshall, 2012; Wheway *et al.*, 2015; Failler *et al.*, 2021), and cell crawling (Cram *et al.*, 2006; Simpson *et al.*, 2008), and then to disrupt them in neurons. A challenge is that because axogenesis can occur immediately following mitosis (Pollarolo *et al.*, 2011), experimental approaches must ensure that mitotic genes can be selectively disrupted in postmitotic cells. For example, one approach to bypass required functions during cytokinesis would be to use conditional somatic CRISPR/CAS9 in *C. elegans* (Tian *et al.*, 2015), which has been used to demonstrate the role of the mitotic scaffolding protein anillin in axonal growth. Another is to use pharmacological agents, such as the Kinesin-5 inhibitor monoastrol, which allows genes to be fully functional until acutely disrupted (Haque *et al.*, 2004). Likewise, optogenetic approaches have great potential because they combine molecular specificity and tight temporal control (Wagner and Glotzer, 2016). More conventionally,

RNAi or CRISPR/CAS9 in cultured neurons or in vivo, where gene expression is inhibited for a prolonged period (Myers and Baas, 2007), may be well suited to study mitotic genes needed for sustained neuronal functioning. These approaches for gene manipulation can be complemented with fluorescent tagging of proteins of interest, as was done to show Rho and Aurora A kinase accumulate at sites of axonal initiation (Pollarolo *et al.*, 2011). In addition, super resolution microscopy and ultrastructural studies can elucidate how the activity of specific proteins contributes to structural architecture (Vassilopoulos *et al.*, 2019).

Ultimately, identification of the genes that are necessary and sufficient for axogenesis will be essential for developing a better understanding of how axons evolved. If the hypothesis that axonal elongation evolved by inducing cytokinesis in an interphase cell is correct, then these genes would be predicted to be closely related to the genes that control cytokinesis. Likewise, if axons evolved through a modification of cell crawling or ciliogenesis, the essential genes for initiating these processes are predicted to be shared. Utilizing phylogenetic approaches to identify genes, paired with molecular genetics to test gene function, offers the promise of making rapid progress on this problem. More broadly, applying this approach to determine the evolutionary relationship between cytokinesis, ciliogenesis, and various modes of motility could help divide the process leading to the evolution of axons into more tractable chunks.

As to why understanding axonal evolution is relevant to human health, Dobzhansky's quote, "Nothing in Biology Makes Sense Except in the Light of Evolution," is apt (Dobzhansky, 1964; Dobzhansky, 1973; Giaimo, 2023). Although effective treatments are limited for neurological trauma and neurodegenerative diseases (Ng and Lee, 2019; Vasic *et al.*, 2019), those with promise involve treatment with neurotrophins, inhibition of Rho, and manipulation of stem cells. Understanding the evolutionary relationship between cell division, crawling, and neuronal function may help explain why these therapies are effective, their off-target effects, and how to better differentiate stem cells into mature neurons. In parallel, an evolutionary link between cell division and neurons may explain why therapies designed to treat cancer can induce neuropathy (Gornstein and Schwarz, 2014; Rivera and Cianfrocca, 2015). Although understanding how axons evolved does not guarantee better approaches for treating cancer and neurological damage, it may provide necessary insights.

SUMMARY

How axons as a structure first evolved is a novel question. Building on the idea that evolution often occurs through the modification of existing features, here, we explore which cellular process is most closely related to axonal elongation. Reviewing the literature on cytokinesis, ciliogenesis, amoeboid migration, mesenchymal migration, neuronal migration, and cell crawling reveals significant overlap in gene expression and physical mechanisms. This suggests the need for a phylogenetic tree to describe their evolutionary relationships. Focusing on axonal elongation, there are strong parallels between axons and cytokinetic bridges, as well as growth cones and the traction force machinery that assists cytokinesis and cell crawling. Currently, this could be attributed to the accumulation of multiple mutations that led to the cooption of genes involved in ciliogenesis, cell division, cell crawling, as well as the de novo creation of new proteins specifically required to form axonal structure. Alternatively, the evolution of axogenesis and growth cone formation could be explained by a small number of events that partially activated cytokinesis in an interphase cell. Looking forward, the next steps will be to rigorously test these hypotheses using statistical/phylogenetic approaches coupled with biophysical analysis and molecular genetic manipulations. Through a better understanding of the evolution of neurons, we believe that novel insights will be gained on how to induce cells to form and elongate axons. More broadly, answering the question of how axons evolved will help determine whether neurons evolved once or independently in comb jellies (*Ctenophores*) and other metazoans. Ultimately, a deeper understanding of axonal evolution may lead to novel treatments for neurodevelopmental disorders, neurotrauma, neurodegeneration, and cancer.

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