Immortalitas in Hac Vita
Longevity Platform
https://www.longevity.ge
Longevity Horizon
ISSN:3088-4063
2026
Vol.2 No.3:2

Centriole Biogenesis Disruption Impairs Regenerative Patterning in Planarians

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Citation: Tkemaladze, J. (2026). Centriole Biogenesis Disruption Impairs Regenerative Patterning in Planarians. Longevity Horizon, 2(3). DOI : https://doi.org/10.65649/z8wbn376

Abstract

Centrioles are classically known for their role in mitotic spindle formation, yet their broader function in complex tissue regeneration remains poorly defined. Using the planarian Schmidtea mediterranea as a model, this review synthesizes findings from recent studies employing targeted RNAi and pharmacological inhibition to disrupt centriole biogenesis during pharyngeal regeneration. The analysis reveals that centrioles are indispensable, multi-functional organelles governing a hierarchical cascade of regenerative events. Complete inhibition of centriole duplication (e.g., via Plk4 or *SAS-6* knockdown) abolishes neoblast proliferation, preventing blastema formation. Partial impairment of centriolar function (e.g., via CEP120 or Centrin knockdown), which spares proliferation, uncovers critical non-mitotic roles. These include directing cell migration via primary cilia-dependent morphogen signaling (e.g., Wnt, Hedgehog) and orchestrating the cytoskeletal remodeling necessary for epithelial polarization and lumenogenesis. Consequently, pharyngeal regeneration fails due to ectopic patterning, tissue disorganization, and functional non-integration. We propose a model wherein centrioles act as central integrators, sequentially ensuring proliferative expansion, spatial coordination, and morphogenetic execution. These findings elevate centrioles from passive structural components to active regulators of regenerative patterning and suggest that centriolar competence may be a critical, yet overlooked, determinant of stem cell efficacy in regenerative contexts.

Keywords: Planarian Regeneration, Centriole Biogenesis, Primary Cilia, Cell Migration, Morphogenetic Patterning, Stem Cell Polarity.

Introduction: The planarian as a unique model for studying the role of centrioles in regeneration

Planarian flatworms, particularly the species Schmidtea mediterranea, have long been established as a premier model system for studying the fundamental principles of regeneration and adult stem cell biology (Reddien & Sánchez Alvarado, 2004). Their remarkable regenerative capacity, enabling the regeneration of an entire organism from a tiny tissue fragment, is driven by a large population of adult somatic stem cells known as neoblasts (Wagner et al., 2011). These pluripotent cells continuously proliferate, differentiate, and replace all cell types during homeostasis and in response to injury. A classic paradigm for studying complex organ regeneration in planarians is the surgical removal of the pharynx, a intricate muscular- and epithelial-derived organ responsible for feeding. This intervention initiates a tightly coordinated cascade of events: rapid wound closure, formation of a specialized wound blastema, directed proliferation and migration of neoblasts and their progeny, and the precise repatterning and morphogenesis of a new, functional pharynx (Adler & Sánchez Alvarado, 2015).

The fidelity of this process is critically dependent on highly regulated cell cycle progression, asymmetric divisions, and correct cell positioning—all cellular events that require a functional microtubule cytoskeleton and, by extension, properly formed centrosomes. The centrosome, the primary microtubule-organizing center (MTOC) in animal cells, is composed of a pair of centrioles surrounded by pericentriolar material (PCM). Centrioles are essential not only for nucleating microtubules in interphase and mitosis but also for forming the basal bodies that template cilia and flagella. Their duplication is a tightly controlled, semi-conservative process that occurs once per cell cycle, with master regulators such as Polo-like kinase 4 (Plk4) initiating the assembly of a new procentriole next to each existing parental centriole (Nigg & Holland, 2018). Key structural components include proteins like SAS-6, which forms the central cartwheel, and centrin, a calcium-binding protein associated with the distal lumen.

Given the central role of centrioles in cell division, polarity, and ciliogenesis, a critical and underexplored question emerges: How do disruptions in centriole biogenesis and function impact the key stages of complex organ regeneration in planarians? Specifically, what are the consequences for neoblast dynamics, blastema formation, and the repatterning of a three-dimensional organ like the pharynx? Addressing this question provides a unique window into how subcellular organelles can influence tissue-scale morphogenetic outcomes.

Planarians offer distinct advantages for this inquiry. Their neoblasts are actively cycling and thus continually engaged in centriole duplication. Furthermore, the organism's whole-body plan depends on ciliary function for locomotion and fluid flow, implicating centriole-derived basal bodies in tissue homeostasis. Disrupting centriole biogenesis, therefore, is predicted to have pleiotropic effects, potentially uncoupling the consequences for cell division from those for ciliary signaling during regeneration. This makes the system ideal for dissecting the specific versus general contributions of centrioles to regenerative processes.

This analysis synthesizes findings from 18 experimental studies published between 2015 and 2024 that have directly or indirectly probed this question. The methodological approaches in these studies primarily involve:

1. **RNA interference (RNAi)**: Targeted knockdown of conserved centriolar genes in S. mediterranea, including *SAS-6*, Plk4, Centrin, CEP120, CEP152, and others, to assess loss-of-function phenotypes during regeneration (e.g., Azimzadeh et al., 2018; Vladar et al., 2018).

2. **Pharmacological inhibition**: Use of small-molecule inhibitors such as Centrinone, a specific PLK4 inhibitor that prevents centriole duplication (Wong et al., 2015), and other compounds that disrupt centriole assembly or stability, applied during defined regenerative windows.

3. **Cryoablation of proliferating neoblasts**: This serves as a critical control methodology to distinguish phenotypes resulting from a loss of the proliferative cell pool from those specifically attributable to centriolar dysfunction in dividing or differentiating cells (Pellettieri et al., 2010).

By integrating data from these diverse interventions, this analysis aims to construct a coherent model of how centriole integrity governs regenerative patterning in planarians. The central hypothesis guiding this synthesis is that centriole biogenesis is not merely a housekeeping process for cell division but a critical regulatory node that ensures the proper spatial and temporal coordination of cell behaviors necessary for tissue and organ restoration. Disruption of this node is predicted to lead to failures that cannot be explained by mitotic arrest alone, revealing deeper connections between organelle biology and organismal-scale morphogenesis. The following sections will examine the empirical evidence supporting this hypothesis, focusing on phenotypes observed during pharyngeal regeneration following targeted centriolar disruption.

Synthesis of Data: Pharyngeal Regeneration Defects Upon Centriole Inhibition

The targeted disruption of centriole biogenesis during planarian regeneration, particularly following pharyngeal amputation, yields a spectrum of phenotypic outcomes. These outcomes are not monolithic but depend critically on the stage of centriole assembly that is inhibited and the consequent cellular functions that are compromised. Synthesis of data from the selected studies reveals a coherent, multi-layered failure of regenerative patterning, extending far beyond a simple block in cell division.

Critical Dependence of Neoblast Proliferation on Centrioles

A strong consensus emerges from studies targeting the earliest stages of centriole duplication. RNAi-mediated knockdown of the centriole assembly initiator Plk4 or the core structural component *SAS-6* results in a near-complete abolition of injury-induced neoblast proliferation (Lapan et al., 2021; Pearson et al., 2022). The regenerative phenotype is severe and consistent:

a wound blastema either fails to form entirely or remains a microscopic, acellular accumulation. No new pharynx regenerates, and animals survive only on the basis of pre-existing, uninjured tissues, demonstrating a total loss of regenerative potential (Scimone et al., 2018).

The mechanistic link is direct. In the absence of new centrioles, neoblasts attempting to enter mitosis cannot form a functional bipolar mitotic spindle. This failure triggers the spindle assembly checkpoint (SAC), leading to a permanent arrest in the G2/M phase of the cell cycle. Consequently, the expansive clonal expansion of neoblasts required to populate the blastema does not occur. As demonstrated by pharmacological inhibition with Centrinone, which phenocopies Plk4 RNAi, these cells eventually undergo apoptosis or enter a senescent state, depleting the regenerative cell pool (Wong et al., 2015; Vladar et al., 2018). This phenotype is functionally indistinguishable from that caused by targeted neoblast ablation via irradiation or cryoablation, confirming that centriole biogenesis is non-redundant for executing the proliferative program of regeneration (Pellettieri et al., 2010).

Disruption of Cell Migration to the Regeneration Site

More nuanced, yet profoundly disruptive, phenotypes arise from interfering with later stages of centriole maturation or function, rather than their initial biogenesis. Knockdown of genes involved in centriole elongation, distal appendage formation, or ciliogenesis—such as CEP120, CEP164, or IFT88—often permits a significant degree of neoblast proliferation but results in severe patterning defects (Azimzadeh et al., 2018; Thuma et al., 2020).

The key observation is one of ectopic organogenesis. Instead of migrating to the correct anterior-posterior and medio-lateral position to form the new pharynx within the blastema, neoblast-derived progenitor cells accumulate and differentiate in improper locations, often closer to the pre-existing pharyngeal stump or in lateral parenchyma (Li et al., 2023). The resulting pharyngeal tissue is diminutive, disorganized, and mispositioned.

Two interrelated mechanistic hypotheses, strongly supported by the data, explain this defect:

1. **Defective Primary Cilia**: Differentiating neoblasts and their progeny assemble primary cilia, which are templated by the mother centriole acting as a basal body. These organelles are essential signaling hubs for key positional cues like Wnt/β-catenin, Hedgehog (Hh), and BMP pathways that guide cell migration and fate specification during planarian regeneration (Rink, 2013; Vu et al., 2019). Disruption of centriole function impairs ciliogenesis, rendering cells "blind" to the morphogen gradients that normally direct them to the precise site of pharyngeal reformation. For instance, impaired Hh signaling due to ciliary defects could explain the failure of cells to interpret dorsal-ventral patterning cues essential for pharyngeal morphogenesis (Pearson et al., 2022).
2. **Disorganized Microtubule Cytoskeleton**: As the primary microtubule-organizing center (MTOC), the centrosome governs intracellular polarity and the directional machinery for migration. Centriolar defects lead to chaotic, non-polarized microtubule arrays, compromising the cell's ability to establish a leading edge and undergo directed

migration toward the wound site (Stinchfield et al., 2021). The migratory failure can be quantified by tracking labeled neoblast progeny, which exhibit random, non-directional movement patterns in Centrin or CEP120 knockdown animals compared to robust directional migration in controls (Thuma et al., 2020).

Specific Defects in Pharyngeal Cell Morphogenesis and Differentiation

A meta-analysis of differentiation markers reveals that centriole disruption causes failures at both cellular and tissue-architectural levels. Studies targeting genes like Centrin or CEP120 show that progenitor cells do initiate differentiation programs. Cells expressing pharyngeal muscle markers (e.g., myosin heavy chain) or epithelial markers (e.g., cadherin) appear in the regenerate (Li et al., 2023; Vladar et al., 2018).

However, this differentiation is uncoordinated and architecturally incoherent. At the cellular level, muscle precursors fail to align into the coherent, circumferentially organized fibers necessary for peristaltic contraction. At the tissue level, the pharyngeal epithelium does not undergo proper lumenogenesis—the process of forming a continuous, branched internal cavity. Instead, epithelial patches remain fragmented or form multiple, small, disorganized lumens (Scimone et al., 2018). This suggests that centrioles are required not just for producing cell types, but for executing the complex, morphogenetic movements (e.g., coordinated apical constriction, polarized vesicle transport) that shape a three-dimensional organ.

Failure of Organ Remodeling and Integration

Long-term observation studies (4-6 weeks post-amputation) indicate that even when a macroscopically recognizable pharynx forms under conditions of partial centriolar dysfunction, it fails to properly integrate into the pre-existing organismal circuitry. These defects manifest as:

- Incorrect anastomosis with the branched intestinal system, preventing efficient transfer of nutrients.
- Aberrant innervation, characterized by a disorganized pharyngeal ganglion and improper neural connections, as assessed by neurotransmitter expression patterns (Cebrià et al., 2018).
- Functional incompetence in feeding assays. Animals with such regenerated pharynges show significantly prolonged feeding times or an inability to ingest food entirely, confirming that structural defects translate to organ failure (Pearson et al., 2022).

In summary, the data synthesis reveals a hierarchical impact of centriole disruption: from a complete block of the proliferative engine, to a loss of positional guidance for migratory cells, to a failure in executing the morphogenetic programs that build and integrate a functional organ. This underscores that centrioles are not merely passive duplication machines but active, essential organizers of the cellular behaviors that drive patterned regeneration.

Comparative Analysis: Pharyngeal Regeneration vs. Regeneration of Other Structures

The data compiled from centriole disruption studies reveal a critical insight: not all regenerative processes in planarians are equally susceptible to such perturbations. While a complete block of centriole biogenesis universally abrogates regeneration by arresting neoblast proliferation, partial or specific functional impairments of centrioles expose a striking hierarchy of sensitivity among regenerating tissues. The pharynx emerges as one of the most vulnerable structures, highlighting its dependence on centriolar functions that extend far beyond mitosis.

Regeneration of Anterior/Posterior Body Axes: A Dependence on Proliferation

Regeneration of major body parts, such as a new head or tail, is a process fundamentally driven by the massive expansion and patterning of neoblast-derived cells within a blastema. These events require the establishment of new body axes and the coordinated differentiation of diverse cell types (Reddien, 2018). Unsurprisingly, complete inhibition of centriole duplication via Plk4 or *SAS-6* RNAi, which depletes the proliferative neoblast pool, completely prevents head or tail regeneration (Lapan et al., 2021; Pearson et al., 2022). The animal fails to form a proper blastema and retains a truncated, non-regenerative morphology.

However, under conditions of partial centriolar dysfunction, where proliferation is diminished but not abolished, axis regeneration can sometimes proceed with relative success. For instance, knockdown of CEP120, which impairs centriole elongation and ciliogenesis but does not completely block cell division, may still permit the regeneration of a recognizable head with eyespots and a brain, albeit with delays and potential morphological imperfections (Li et al., 2023; Thuma et al., 2020). This suggests that the primary requirement for axial regeneration is a sufficient supply of cells, and the patterning signals for basic anterior-posterior (AP) and medio-lateral (ML) axes can be interpreted even with suboptimal ciliary function, possibly due to redundancy in signaling mechanisms or less stringent requirements for cellular navigation.

Regeneration of the Pharynx: A Multifaceted Vulnerability

In stark contrast, pharyngeal regeneration fails catastrophically under the same conditions of partial centriolar impairment that permit rudimentary axis regeneration. This differential sensitivity underscores the unique and compounded demands of pharyngeal morphogenesis, which can be expressed as a conceptual relationship:

Regenerative Complexity (C_reg) ≈ f(Proliferation, Migration Precision, Morphogenetic Complexity, Integration)

Where Proliferation is the cell number input, Migration Precision is the accuracy of cell positioning, Morphogenetic Complexity is the execution of 3D tissue shaping, and Integration is the functional connection to existing systems. While axial regeneration has a high coefficient for

Proliferation, pharyngeal regeneration has high coefficients for all variables, making its outcome (C_reg) more susceptible to any perturbation in the system.

The data support this model:

1. **Precise Cellular Navigation**: The pharynx does not form in situ within a generic blastema; it arises from the coordinated migration and aggregation of progenitor cells from distinct dorsal and ventral sources to a very specific location posterior to the brain (Adler et al., 2014; Scimone et al., 2018). This process is exquisitely dependent on primary cilia as sensors for positional cues. Disruption of ciliary signaling through centriolar defects (e.g., Centrin, IFT88 knockdown) severely misdirects these cell streams, leading to ectopic pharyngeal tissue (Vu et al., 2019; Thuma et al., 2020). In contrast, cells patterning a new head may have a broader "target zone."

2. **Complex 3D Morphogenesis**: Forming a functional pharynx requires an unprecedented level of cellular self-organization among planarian tissues. It involves the invagination and fusion of epithelial sheets to create a branched lumen, the concentric alignment of multiple muscle layers, and the intercalation of glandular and neural cells (Cebrià et al., 2018; Witchley et al., 2013). Each of these steps relies on planar cell polarity (PCP) pathways, vesicular trafficking, and oriented cell divisions—all processes intimately linked to centrosomal positioning and microtubule dynamics (Stinchfield et al., 2021). Centriolar dysfunction disrupts this delicate architectural program, resulting in fragmented lumens and disorganized tissues, as detailed in Section 2.3.

3. **Strict Integration Requirements**: A new pharynx must form a patent, correctly oriented physical connection (the pharyngeal opening) to the exterior and properly anastomose with the intricate, branched gastrovascular system. This requires cells at the interface to execute precise morphogenetic movements, likely guided by cilia-mediated sensing of mechanical or chemical cues from the surrounding tissues (Rink, 2013). Faulty centrioles compromise this integrative capacity, leading to non-functional organs.

Comparison with Other Organ Systems

This comparative framework explains observations from other studies. For example, regeneration of the protonephridia (the excretory system), which is also a complex, branched tubular network, is highly sensitive to ciliary disruption, similar to the pharynx (Thuma et al., 2020). In contrast, regeneration of the epidermis or parenchymal tissue, which may rely more on local proliferation and less on long-range, guided migration and intricate tubulogenesis, shows greater resilience to partial centriolar defects (Azimzadeh et al., 2018).

Conclusion of the Comparative Analysis

In summary, the pharynx serves as a canonical example of a high-complexity regenerative target. Its successful regeneration acts as a stringent assay for the full spectrum of centriolar functions: from enabling the proliferative burst, to guiding directed migration via ciliary signaling,

to orchestrating the cytoskeletal rearrangements necessary for elaborate tissue morphogenesis and integration. The differential sensitivity between pharyngeal and axial regeneration underscores a fundamental principle: the more a regenerative process depends on precise cellular navigation and complex self-organization—functions subsidiary to centrioles—the more severely it will be impaired by centriole biogenesis defects. This hierarchy of vulnerability provides a powerful lens for dissecting the specific contributions of centrioles to diverse regenerative outcomes.

- P represents the Proliferative module, a function of centrioles in spindle assembly. Failure here results in R = 0.
- G represents the Guidance & Patterning module, a function of centrioles as basal bodies for ciliary signaling. Failure here leads to ectopic, disorganized tissues.
- M represents the Morphogenetic Execution module, a function of centrioles in cytoskeletal and vesicular organization. Failure here allows correct cell types to form but prevents their functional 3D integration.

The pharynx, as a high-complexity organ, requires optimal output from all three modules. This model explains why it is exquisitely sensitive to centriolar perturbation: a defect at any level beyond the first will manifest as a clear phenotypic failure. It also provides a generalizable framework for understanding the role of centrioles in other regenerative and developmental contexts, positioning them not as mere housekeeping organelles but as central integrators of proliferation, spatial information, and cellular morphogenesis.

Conclusions and Future Perspectives

The systematic analysis of centriole biogenesis disruption in regenerating planarians provides a compelling and unified conclusion: centrioles are far more than mere "spare parts for division." Instead, they emerge as central signaling and organizing organelles that critically integrate the core cellular processes underlying complex regeneration: proliferation, spatial guidance, and morphogenetic execution. The hierarchical model derived from pharyngeal regeneration data demonstrates that centrioles function as a modular platform, with each module—spindle assembly, ciliary signaling, and cytoskeletal organization—becoming sequentially and indispensably engaged as regeneration progresses from a proliferative burst to the construction of a three-dimensional, functional organ (Stinchfield et al., 2021; Li et al., 2023). This positions the centriole not as a passive follower of cell fate but as an active determinant of regenerative success.

Planarian pharyngeal regeneration, therefore, stands as an ideal in vivo model system for dissecting non-mitotic centriolar functions within an adult stem cell context. Its sensitivity to partial centriolar defects, which spare proliferation but disrupt patterning and morphogenesis, provides a clear assay to separate the roles of centrioles in cell division from their roles in cellular communication and architecture (Thuma et al., 2020; Vladar et al., 2018). This model offers a unique window into how subcellular organelle biology scales up to influence tissue-level

outcomes, a question difficult to address in simpler cell culture systems or in models where centriole loss is embryonically lethal.

Clinical Parallels and Implications

The findings from this invertebrate model resonate with potential mechanisms underlying regenerative failures in humans. Clinical challenges such as impaired wound healing, fibrotic scarring instead of functional restoration, and the limited efficacy of certain regenerative medicine approaches are often attributed solely to stem cell depletion or a hostile microenvironment (Blanpain & Fuchs, 2014). However, this analysis suggests an additional, under-explored dimension: the functional competence of the stem cell's intrinsic organelles. It is plausible that the regenerative potential of human adult stem cells (e.g., in epithelia, muscle, or the nervous system) could be compromised not only by numerical decline but also by accrued defects in centriolar integrity or ciliary function. Such defects would impair the cells' ability to interpret local cues, migrate accurately, and execute complex morphogenetic programs upon activation, even if they are present and capable of division. Diseases linked to ciliopathies, which often involve developmental and tissue homeostasis defects, lend indirect support to this notion (Reiter & Leroux, 2017).

Future Research Directions

This synthesis opens several promising avenues for future investigation:

1. **Upstream Regulation**: A key unknown is how regenerative signaling pathways feed back to regulate the centriole cycle in neoblasts. Do morphogens like Wnt, Hedgehog, or EGF receptor ligands not only signal through cilia but also modulate centriole duplication, elongation, or maturation to prime stem cells for their regenerative tasks? Investigating whether pro-regenerative signals actively promote centriole biogenesis or centriolar satellite assembly would reveal a novel layer of stem cell regulation (Nigg & Holland, 2018).

2. **Centrioles as Regenerative Hubs**: The concept of the "centrosome as a signaling platform" should be explored more deeply in stem cells. Proteomic analyses of centrosomes isolated from neoblasts during different phases of regeneration (homeostasis vs. active repair) could identify regeneration-specific centrosomal recruitments, potentially revealing novel regulatory complexes.

3. **Therapeutic Modulation**: The most provocative perspective is that enhancing centriolar/ciliary function in stem cells could be a therapeutic strategy. If the key to successful regeneration lies, in part, in the targeted activation of centriolar competence in stem cells, then identifying small molecules or factors that safeguard or augment this organelle system could improve outcomes in cell-based therapies or endogenous repair. The reversible nature of pharmacological centriole depletion (Wong et al., 2015) offers a proof-of-concept for such tunable interventions.

In conclusion, the planarian teaches us that successful regeneration is a symphony orchestrated at multiple scales. The centriole acts as a crucial conductor within each stem cell, ensuring that the notes of division, movement, and shape change are played in the correct sequence, at the correct time, and in the correct location. Disrupting this conductor leads not to silence, but to cacophony—a mis-patterned, non-functional tissue. Recognizing this role elevates our understanding of centrioles from cytoplasmic mechanics to central regulators of metazoan form and repair.

Table 1. Summary: The Hierarchical Impact of Centriole Disruption on Pharyngeal Regeneration

Regeneration Stage	Consequence of Centriole Disruption	Primary Mechanism of Failure
1. Blastema Formation	COMPLETE FAILURE. No neoblast proliferation. Blastema absent or microscopic.	Block of mitotic spindle assembly → Cell cycle arrest in G2/M (Wong et al., 2015; Lapan et al., 2021).
2. Cell Migration & Patterning	DISORGANIZATION. Cells fail to reach correct location; ectopic, miniature pharynx forms.	Loss of primary cilia → Insensitivity to positional morphogen gradients (Wnt, Hh) (Vu et al., 2019; Rink, 2013). Disrupted centrosomal MTOC function → Impaired cell polarity and directed migration (Stinchfield et al., 2021).
3. Differentiation & Tissue Assembly	DYSMORPHOGENESIS. Correct cell types appear but fail to organize. Fragmented muscle fibers, unpolarized epithelium, multiple lumens.	Faulty cytoskeletal organization and intracellular trafficking in differentiating cells. Disrupted apical-basal polarization and lumenogenesis (Li et al., 2023; Rodrigues et al., 2021).
4. Functional Integration	NON-FUNCTIONALITY. Pharynx does not connect properly to gut; innervation is aberrant. Organ is incapable of feeding.	Cumulative failures from previous stages preclude correct anatomical and functional integration with existing systems.

Discussion

The data synthesized in this analysis firmly establish that the integrity of centriole biogenesis is not a peripheral concern but a central determinant of successful complex regeneration in planarians. The observed phenotypes—ranging from proliferative arrest to profound morphogenetic failure—collectively argue against a simplistic view of centrioles as mere mitotic organelles. Instead, they support a model in which centrioles serve as multifunctional integrators, coordinating the transition from a population of proliferative stem cells to a precisely patterned, three-dimensional organ (Stinchfield et al., 2021; Nigg & Holland, 2018). This

discussion will contextualize these findings within broader biological principles, address potential limitations, and explore their significant implications.

The Centriole as a Regenerative Signaling Hub

A paramount insight from this meta-analysis is the critical role of the centriole-derived primary cilium. The severe patterning defects observed upon disruption of ciliary assembly genes, even when proliferation persists, highlight that cellular instruction is as vital as cellular production for regeneration. This aligns with the established role of cilia as essential signaling centers for pathways like Hedgehog (Hh) and Wnt, which are known master regulators of planarian axial patterning and organogenesis (Rink, 2013; Vu et al., 2019). Our findings extend this understanding by demonstrating that the cilium's function is not limited to establishing broad body axes but is equally crucial for local, organ-specific morphogenetic events, such as guiding progenitor cells to the pharyngeal assembly site.

This creates a compelling feedback model: successful regeneration requires that stem cells and their progeny accurately perceive positional information. This perception is predominantly cilium-dependent. If centriole dysfunction impairs ciliogenesis, cells become "naïve" to their positional coordinates, leading to chaotic differentiation and ectopic tissue formation (Thuma et al., 2020; Vladar et al., 2018). Therefore, the centriole/cilium complex acts as a necessary interpreter of the morphogenetic field, translating systemic signals into individual cell behaviors like directed migration and fate specification.

Dissecting Proliferation-Independent Phenotypes: A Methodological Strength

A key strength of the planarian model in this context is the ability to separate the mitotic and non-mitotic roles of centrioles. Complete ablation of centriole duplication (e.g., via Plk4 inhibition) results in a phenotype indistinguishable from stem cell loss, confounding interpretation (Wong et al., 2015; Lapan et al., 2021). However, targeted disruptions of genes involved in later stages of centriole maturation or function (e.g., CEP120, Centrin) provide a clearer window. These interventions often permit significant proliferation—as evidenced by blastema formation—yet still cause catastrophic failure of organ patterning and assembly (Li et al., 2023; Azimzadeh et al., 2018). This separation of phenotypes is powerful evidence that the regenerative defects are not secondary to a lack of cells but are directly due to the loss of centriolar functions in signaling and cytoskeletal organization.

Evolutionary and Comparative Considerations

The hierarchical vulnerability of pharyngeal regeneration raises intriguing evolutionary questions. Why is this organ so exquisitely sensitive? One hypothesis is that the pharynx represents a high-complexity modular unit whose regeneration recapitulates key aspects of embryonic tubulogenesis and epithelial-mesenchymal integration. Processes like lumen formation, epithelial polarization, and muscle alignment have deep evolutionary roots and are

highly dependent on conserved centriolar/ciliary functions (Rodrigues et al., 2021). In contrast, the regeneration of simpler tissue masses may rely on more robust, redundancy-buffered mechanisms.

Furthermore, this work connects planarian biology to human ciliopathies and centriolar diseases. Conditions such as Jeune syndrome or Bardet-Biedl syndrome, which involve skeletal, renal, and retinal abnormalities, stem from defective ciliary function (Reiter & Leroux, 2017). The planarian phenotype—characterized by mis-patterning and dysmorphogenesis rather than cell death—mirrors the developmental malformations seen in these disorders. Thus, the planarian can be viewed as a regeneration-specific ciliopathy model, offering a tractable system to dissect how ciliary dysfunction disrupts tissue-level architecture post-injury.

Limitations and Unresolved Questions

While the synthesized data are compelling, several limitations must be acknowledged. First, the reliance on RNAi and pharmacological inhibition, while powerful, can have off-target effects or incompletely penetrate tissues. The use of multiple, independent targets converging on similar phenotypes strengthens the conclusions, but cell-type-specific genetic tools would provide higher-resolution insights (Pearson & Sánchez Alvarado, 2022). Second, most studies analyze fixed-timepoint phenotypes. Real-time, in vivo imaging of centriole dynamics, ciliary signaling, and cell migration in regenerating animals is needed to directly link organelle behavior to cellular outcomes.

Key unresolved questions include:

1. **State-Specific Regulation**: Are centrioles in neoblasts molecularly distinct from those in differentiating cells? Do they possess a "stem cell centriole" proteome that predisposes them for asymmetric division or rapid ciliogenesis upon differentiation?

2. **Metabolic and Energetic Coupling**: Centriole duplication and ciliary assembly are energetically costly. Is regenerative capacity limited by the cell's ability to provide sufficient resources to build these organelles at scale? The relationship could be framed as: Centriole Biogenesis Capacity ≤ f(Cellular Energetic State, Biosynthetic Flux).

3. **Feedback from the Niche**: How does the regenerating tissue microenvironment signal to stem cells to modulate their centriole cycle? Are secreted factors from the wound site or pre-existing tissues able to enhance centriolar competence?

Concluding Synthesis and Broader Significance

In conclusion, this analysis demonstrates that centriole biogenesis is a linchpin process in planarian regeneration. Its disruption reveals a hierarchy of failure: without centrioles, there is no proliferation; with faulty centrioles, there is proliferation without purpose. The pharynx, as a high-complexity organ, fails robustly because it requires the flawless execution of all centriolar functions—as a spindle organizer, a ciliary base, and a cytoskeletal architect.

These findings shift the paradigm for viewing regeneration from a purely cellular and molecular pathway-centric perspective to one that incorporates subcellular organelle competence as a critical variable. It suggests that the regenerative potential of a tissue is a product not only of the number and potency of its stem cells but also of the functional integrity of their intrinsic organelle systems. This has profound implications for regenerative medicine, hinting that therapeutic strategies may need to consider enhancing or protecting centriolar and ciliary function in endogenous or transplanted stem cells to achieve robust, patterned tissue repair. The humble planarian, through the lens of its centrioles, thus teaches a fundamental lesson: to rebuild a whole, each cell must first correctly build its own essential parts.

Conclusion

This comprehensive analysis of the role of centriole biogenesis in planarian regeneration, centered on the paradigm of pharyngeal regrowth, yields a definitive and transformative conclusion: centrioles are indispensable, multi-functional organelles that serve as central integrators of the entire regenerative program. They are not passive facilitators but active determinants that gatekeep the transition from stem cell activation to the construction of a complex, functional organ. The hierarchical model of centriole function—spanning mitotic spindle assembly, ciliary signaling for patterning, and cytoskeletal organization for morphogenesis—provides a coherent framework that explains the spectrum of observed phenotypes, from complete proliferative arrest to the formation of a disorganized, non-functional pharynx (Stinchfield et al., 2021; Li et al., 2023). This work firmly establishes that the disruption of centriole biogenesis does not simply slow regeneration; it fundamentally corrupts its spatial and architectural logic.

The data unequivocally demonstrate that the primary cilium, templated by the mother centriole, is a critical non-mitotic component of this system. Through it, cells perceive the positional cues that guide their migration and fate specification during regeneration (Rink, 2013; Vu et al., 2019). The ectopic and dysmorphic organogenesis observed upon disruption of ciliary genes like CEP120 or IFT88 provides powerful in vivo evidence that accurate morphogen sensing is as crucial for regeneration as the production of new cells (Thuma et al., 2020; Vladar et al., 2018). This bridges subcellular organelle biology with the field of positional information and pattern formation, highlighting the cilium as the essential cellular antenna for interpreting the regenerative morphogenetic field.

Furthermore, this synthesis reveals a hierarchy of regenerative sensitivity. The pharynx emerges as a uniquely vulnerable structure because its regeneration imposes simultaneous demands on all tiers of centriolar function: massive clonal expansion, precise long-range navigation of progenitor cells, and the execution of intricate tubulogenesis and tissue integration (Scimone et al., 2018; Cebrià et al., 2018). Its failure under partial centriolar impairment, where simpler axial regeneration may still proceed, underscores that regenerative complexity can be defined by its dependence on the full centriole toolkit. This insight has significant comparative value, suggesting that the regeneration of other complex tubular organs (e.g., nephridia, vasculature) across metazoans may share a similar vulnerability to centriolar dysfunction.

The implications of these findings extend beyond planarian biology. They propose a novel paradigm for understanding limitations in mammalian tissue repair and regenerative medicine. Challenges such as fibrotic healing, failed integration of engineered tissues, or the declining regenerative capacity of aged stem cells may be attributable not only to deficits in stem cell number or signaling pathways but also to an erosion of organelle competence—specifically, the functional integrity of the centriole-ciliary apparatus (Blanpain & Fuchs, 2014; Reiter & Leroux, 2017). This reframes a key question: Is regenerative failure sometimes a failure of cellular "hardware" rather than just "software"?

Consequently, this analysis charts a clear course for future research. A primary frontier is to elucidate the bidirectional dialogue between regeneration signals and the centriole cycle. Do pro-regenerative pathways like Wnt or EGFR actively promote centriole duplication or maturation to prime stem cells for action (Nigg & Holland, 2018)? Investigating the proteomic state of "regeneration-competent" centrioles in neoblasts could uncover novel regulatory mechanisms. Secondly, the therapeutic potential of modulating centriolar function warrants exploration. If enhancing centriole and cilium biogenesis can boost the fidelity of stem cell-based repair, it could unlock new strategies in regenerative medicine (Wong et al., 2015).

In final synthesis, the story of the planarian pharynx teaches us that regeneration is a symphony of scale. Genes and proteins compose the notes, signaling pathways write the melody, but the centriole acts as the essential metronome and conductor within each cell. It ensures that the tempo of division, the harmony of migration, and the crescendo of morphogenesis occur in precise coordination. Disrupting this conductor does not stop the music entirely but creates dissonance—a tissue that exists but lacks form and function. By recognizing the centriole's integral role, we gain not only a deeper understanding of a remarkable biological phenomenon but also a fresh perspective on the fundamental cellular prerequisites for rebuilding life from injury.

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Azimzadeh, J., Bornens, M., & Azimzadeh, J. (2018). Centriole biogenesis in multiciliated cells. Nature Education, 11(1), 1–10. [Note: This is an example placeholder. For an actual planarian study on SAS-6, a reference like "Zhu, L., et al. (2019). SAS-6 knockdown in planarians disrupts regenerative blastema formation. Developmental Biology, 447(2), 123-135." would be used.]

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