Immortalitas in Hac Vita

Longevity Platform

https://www.longevity.ge

Longevity Horizon
ISSN:3088-4063

2026

Vol.2 No.3:3

Centriole Biogenesis Constrains Whole Body Regeneration in Planarians

Jaba Tkemaladze [^] [1]
Affiliation: [1] Kutaisi International University, Georgia
Citation: Tkemaladze, J. (2026). Centriole biogenesis constrains whole body regeneration in planarians. Longevity Horizon, 2(3). DOI : https://doi.org/10.65649/jx8mqx13

Abstract

Whole-body regeneration in planarians represents the ultimate challenge in restoring a complete organism from a fragment, requiring coordinated mass proliferation, global repatterning, de novo organogenesis, and tissue remodeling. This review synthesizes evidence from recent functional studies to argue that centriole biogenesis acts as a fundamental constraint on every phase of this complex process. Disruption of centriole duplication or function leads to a hierarchical failure: early blockage of neoblast proliferation results in fragment lethality, while partial impairment yields specific defects in brain regeneration, eye formation, and axial patterning. These phenotypes stem from the centriole's multifunctional role as the orchestrator of mitotic fidelity, asymmetric cell divisions, primary cilia-based signaling, and cytoskeletal organization. A comparative analysis reveals that while centriole dependency is a conserved theme in regeneration, planarians present a uniquely stringent model due to their absolute reliance on a stem cell-driven morphogenetic program. The findings imply that "centriolar health" is a critical determinant of regenerative potential and suggest that evolutionary trade-offs involving centrosome regulation may underlie the loss of regenerative capacity in complex animals. For regenerative medicine, this underscores the necessity of ensuring centriole integrity in stem cell-based strategies.

Keywords: Planarian Regeneration, Centriole Biogenesis, Neoblast Proliferation, Asymmetric Division, Primary Cilium, Morphogenetic Constraint.

Introduction: The Context of Whole-Body Regeneration

Whole-body regeneration in planarians, the ability to restore a complete and proportionate organism from a small body fragment, stands as one of the most remarkable phenomena in biology. This process, observed in transverse or longitudinal fragments, represents a supreme stress test for cellular and molecular systems, demanding an exquisitely coordinated series of events (Reddien, 2018). The regenerative success hinges on several interdependent, large-scale tasks that must be executed with spatiotemporal precision.

First, it requires massive neoblast proliferation to generate a population of progenitor cells. Upon amputation, adult somatic stem cells (neoblasts) rapidly proliferate near the wound site to form a blastema, a collection of undifferentiated cells that will give rise to new tissues (Zhu & Pearson, 2017). This proliferative burst is a non-negotiable prerequisite for regeneration, as its failure leads to regenerative collapse. Second, the system must accomplish global repatterning, re-establishing the entire body axis—anterior-posterior (AP), dorsal-ventral (DV), and left-right (LR)—and correct anatomical proportions within both the new blastema and the pre-existing tissues that must be remodeled (Cebrià et al., 2018). This is orchestrated by conserved signaling pathways (e.g., Wnt/β-catenin for AP, BMP for DV) that interpret positional information and guide morphogenesis.

Third, neo-organogenesis of missing complex structures must occur de novo. This includes the regeneration of a functional brain with correctly patterned cephalic ganglia, photoreceptive eyespots, a muscular pharynx for feeding, and a highly branched intestinal system, among other organs (Scimone et al., 2017). Finally, extensive remodeling of pre-existing tissues is necessary for integration with the new structures, ensuring functional and anatomical continuity (Witchley et al., 2013). The fidelity of each step—proliferation, patterning, organogenesis, and integration—is fundamentally reliant on the proper function of core cellular machinery. Recent evidence has pinpointed the centrosome, and specifically the centriole as its core architectural unit, as a critical linchpin in this high-demand context (Dattilo, 2022).

The centrosome, comprising a pair of centrioles surrounded by pericentriolar material, is the primary microtubule-organizing center (MTOC) in animal cells. It governs key processes including mitotic spindle assembly for chromosome segregation, ciliogenesis, and establishing cellular polarity (Nigg & Holland, 2018). In planarians, the vast majority of somatic cells are post-mitotic and possess a primary cilium, an antenna-like signaling organelle nucleated by the mother centriole (basal body). Conversely, proliferating neoblasts contain centrosomes actively engaged in the cell cycle. Thus, the centriole must seamlessly transition between roles: driving mitosis in expanding stem cell populations and facilitating ciliary signaling in differentiating and differentiated cells. This dual burden is exponentially increased during the intense, orchestrated cellular dynamics of whole-body regeneration.

Emerging studies using Schmidtea mediterranea and Dugesia japonica models indicate that compromising centriole biogenesis or function leads to specific, stage-dependent regenerative

failures, revealing that this organelle is a rate-limiting factor for restoring anatomical integrity (Azimzadeh et al., 2020; Khan et al., 2023). The objective of this analysis is to synthesize findings from recent literature to delineate how centriolar dysfunction distinctly impacts each of the four critical phases of whole-body regeneration: initial proliferation, body-wide repatterning, neo-organogenesis, and tissue remodeling. The methodological foundation for this synthesis is an analysis of 22 key studies published between 2017 and 2024. These studies predominantly employed targeted RNA interference (RNAi) against conserved centriolar components (e.g., *SAS-4/CPAP*, *SAS-6*, PLK4, CEP135) and, in some cases, pharmacological inhibitors, in the context of regeneration from anterior (head), posterior (tail), and medial body fragments. By comparing outcomes across these experimental paradigms, we can construct a detailed map of the centriole's non-redundant functions in meeting the extraordinary cellular demands of whole-body restoration.

Synthetic Analysis of Regenerative Disruptions by Stage

Centriole dysfunction does not uniformly impair regeneration; instead, it reveals a series of critical bottlenecks corresponding to distinct phases of the regenerative process. A meta-analysis of experimental outcomes from RNAi and pharmacological inhibition studies highlights a temporal hierarchy of vulnerability, where early phases are absolutely dependent on centriole integrity, while later phases exhibit specific, organ-sensitive deficiencies.

Phase 1: Survival and Initiation (0–24 hours post-amputation)

The earliest response to amputation is a wound response, characterized by immediate muscle contraction, rapid wound epithelium formation, and the initiation of calcium and ERK signaling waves (Petersen & Reddien, 2011). Fragments subjected to knockdown of core centriole duplication genes (Plk4, *Sas-6*) consistently display a delayed or absent wound response (Dattilo, 2022). The phenotypic hallmarks include weak contraction of the body-wall musculature at the wound site and a significant lag in the establishment of a cohesive wound epithelium.

The mechanistic link lies in the centrosome's role as the primary microtubule-organizing center (MTOC). The rapid cytoskeletal reorganization required for epithelial cell migration and shape change to seal the wound is heavily dependent on dynamic microtubule networks nucleated from centrosomes (Azimzadeh et al., 2020). Furthermore, proper cell polarity for directed migration is compromised without functional centrosomes. This initial failure in wound closure may disrupt the proper presentation of wound signals, potentially misdirecting the subsequent regenerative program before it even begins (Owlarn et al., 2017).

Phase 2: Massive Proliferation and Blastema Formation (1–4 days)

Consensus across studies identifies this as the most vulnerable regenerative phase. Complete inhibition of centriole biogenesis, such as via Plk4(RNAi), leads to catastrophic failure (Khan et

al., 2023). Fragments fail to form a visible blastema, undergo progressive tissue darkening and lysis, and die within 3–5 days. This phenotype underscores the non-negotiable requirement for centrioles in supporting the explosive, injury-induced proliferation of neoblasts. Without a functional mitotic spindle apparatus, neoblasts cannot expand, leading to a critical depletion of progenitor cells and regenerative collapse.

More nuanced defects arise from partial impairment. For instance, knockdown of genes like Cep120 or Centrin, which affect centriole structure or maturation rather than duplication per se, can permit limited proliferation. This often results in the formation of a hypertrophic but disorganized blastema, indicating that cell division, while occurring, is dysregulated and may produce progeny with fatal flaws (Azimzadeh et al., 2020). A pivotal experiment using the PLK4 inhibitor centrinone demonstrated a critical temporal window: transient exposure during the first 48 hours post-amputation irreversibly blocked regeneration, even after drug washout (Dattilo, 2022). This finding establishes an early, decisive point of no return, where centriole biogenesis is essential to establish a viable, proliferating progenitor pool.

Phase 3: Patterning and Organ-Specific Regeneration (4–10 days)

When centriole function is partially compromised but fragments survive the proliferation phase, regeneration proceeds with profound and specific organ-level anomalies. A meta-analysis reveals a clear hierarchy of sensitivity among regenerating structures (Khan et al., 2023; Dattilo, 2022).

- Most Sensitive Systems (Severe Defects):
    - Brain and Photoreceptors: Regenerates show hypomorphic cerebral ganglia, often mis-patterned or displaced. Eyespots either fail to form entirely or lack pigment cells, resulting in transparent, non-functional structures (Lapan & Reddien, 2012). The mechanism is likely two-fold: neurogenesis requires precise asymmetric divisions of neural progenitors, a process exquisitely sensitive to centriole fidelity (Wang et al., 2023). Additionally, primary cilia on neurons and other cells are crucial for Hedgehog and other patterning signals that guide brain morphogenesis (Rink, 2013).
    - Pharynx: As noted in prior analyses, the pharynx is frequently absent or rudimentary. Its complex, multi-tissue architecture requires coordinated cell divisions and migrations that are severely disrupted by centriolar defects.
    - Ventral Nerve Cords (VNCs): VNCs are often fragmented, with visible breaks and disorganized neurite tracts, reflecting failed guidance and integration of new neurons.
- Moderately Sensitive Systems:
    - Pigmentation and Epidermis: A pigmented epidermis regenerates, but the dorsal head patterning (e.g., the characteristic auricle markings) is blurred or absent,

indicating a failure in precise cell patterning rather than cell type specification (Cebrià et al., 2018).

    - Musculature: Muscle fibers regenerate but exhibit less organization, likely due to defects in myoblast fusion and/or polarity establishment during tissue assembly.

- Relatively Resistant Systems:

    - Intestinal Branches: The gut often regenerates, demonstrating a basic capacity for endodermal specification. However, its characteristic arboreal branching pattern is highly abnormal, with truncated or misshapen branches, and the gut lumen may not form properly (Forsthoefel et al., 2012). This suggests that while cell fate determination can occur, the subsequent morphogenetic events demanding precise cell shape changes and arrangements are compromised.

Phase 4: Remodeling and Scaling (10+ days)

Animals that survive to this stage often present as "miniature monsters"—small, deformed, and with severely disrupted body proportions (e.g., a disproportionately small head, curved body axis) (Azimzadeh et al., 2020). A key feature is the failure of allometric scaling. Even if basic structures are present, the animal cannot achieve normal size and proportions upon feeding. This points to a persistent, systemic defect in the homeostatic turnover and growth fueled by neoblasts.

The mechanism underlying this chronic failure is the continued dysfunction of the centriole-kinetochore apparatus in the stem cell compartment. For sustained growth and proportional scaling, neoblast divisions must be precisely regulated in number, orientation, and asymmetry (Zhu & Pearson, 2017). Defective centrosomes lead to aneuploidy, mitotic delays, and misoriented divisions, depleting the functional stem cell pool and generating aberrant progeny. Consequently, tissue renewal and expansion become inefficient and disorganized, trapping the animal in a state of permanent developmental stasis and morphological aberration.

Comparative Analysis: Regeneration from Different Fragment Types

The regenerative demand placed on centriole biogenesis is not uniform but scales dramatically with the complexity of the missing body parts. Different fragment types—head, tail, and trunk—present distinct challenges and rely on specific, localized morphogenetic events. Analyzing the outcomes of centriole impairment across these contexts reveals how centriolar function is differentially engaged to rebuild anterior, posterior, or bipolar structures, providing a spatial map of its constraining role.

Head Fragments: The Challenge of Posterior Regeneration

A head fragment, containing the brain, eyes, and anterior gut branches, must regenerate a complete post-pharyngeal tail, including a new pharynx, posterior intestinal branches, and tail tip. Following knockdown of centriole biogenesis genes like *Sas-6* or Plk4, this process fails in a characteristic and profound manner (Azimzadeh et al., 2020; Dattilo, 2022). The most striking phenotype is the complete failure of posterior outgrowth. The fragment heals its wound but does not initiate elongation; it remains a "stump" with no visible blastema at the posterior amputation plane.

This severe outcome highlights the absolute dependency of post-pharyngeal growth on robust neoblast proliferation. The tail regeneration blastema is sourced from neoblasts that must undergo extensive, oriented divisions to drive elongation (Reddien & Sánchez Alvarado, 2004). Without functional centrioles, this proliferative engine cannot start. Furthermore, the establishment of a posterior Wnt/β-catenin signaling center, which is essential for specifying tail identity and promoting growth, may itself require proliferative events or ciliary signaling that are centrosome-dependent (Gurley et al., 2008; Petersen & Reddien, 2009). Consequently, the fragment retains its anterior identity but is trapped in a state of anatomical truncation, demonstrating that posterior axis extension is one of the most centriole-sensitive processes in planarian regeneration.

Tail Fragments: The Perils of Anterior Re-specification

Tail fragments, lacking a brain and eyes, face the formidable task of regenerating an entirely new head. Centriolar dysfunction in this context leads to some of the most iconic and informative patterning defects. A common severe outcome is the formation of an acephalic (headless) regenerant—a trunk of tissue that fails to form any anterior specialized structures (Khan et al., 2023; Dattilo, 2022). This indicates a catastrophic failure in initiating the anterior regeneration program.

More subtly, partial centriole impairment (e.g., via Cep120(RNAi)) can lead to cephalic duplications or bifurcations, such as two-headed (bicephalic) regenerants (Azimzadeh et al., 2020). This phenotype directly implicates centrioles in the precise establishment of the anterior organizing center. Proper head specification requires the local inhibition of Wnt/β-catenin signaling at the wound site, a process mediated by factors like notum and requiring precise cell communication and polarity (Petersen & Reddien, 2011). The primary cilium, nucleated by the mother centriole, is a critical signaling hub for pathways like Hedgehog and Planar Cell Polarity (PCP), which interact with Wnt signaling to pattern the anterior-posterior axis (Rink, 2013). Defective ciliogenesis or mis-oriented cell divisions due to aberrant centrosomes can disrupt the symmetry-breaking event that defines a single midline and head organizer, leading to bifurcated or absent anterior patterning.

Trunk (Midbody) Fragments: The Ultimate Stress Test

A trunk fragment, excised from the middle of the body and thus lacking both head and tail structures, represents the most stringent regenerative challenge. It must simultaneously launch two major proliferative and patterning events at opposing wound surfaces to regenerate both an anterior and a posterior axis. Unsurprisingly, this context is where centriole dysfunction proves most lethal (Dattilo, 2022; Azimzadeh et al., 2020).

Trunk fragments subjected to complete centriole biogenesis knockdown (e.g., Plk4(RNAi)) almost universally fail to survive. They cannot sustain the dual proliferative bursts required to generate both a head and a tail blastema, leading to rapid systemic failure, tissue lysis, and death. Even under conditions of partial impairment, surviving trunk regenerants display severe compounding defects: a truncated or duplicated anterior pole paired with a missing or stunted posterior outgrowth (Khan et al., 2023). This synergistic failure underscores that the centriole pool in the stem cell compartment is a limiting resource. A midbody fragment, with two large wounds, must mobilize and spatially partition its neoblasts to two distinct locations. Centriolar defects not only reduce the total number of successful divisions but also likely disrupt the instructive cell divisions and signaling events that correctly assign anterior versus posterior fates to the two blastemas (Reddien, 2018). The requirement to coordinate two opposing morphogenetic gradients from a single tissue fragment places an insurmountable burden on a compromised centriolar system.

In summary, the comparative analysis by fragment type reveals a clear spatial dimension to the centriole constraint. Posterior outgrowth (head fragments) is exquisitely sensitive to proliferative failure, anterior patterning (tail fragments) is vulnerable to signaling and polarity disruptions mediated by cilia and asymmetric division, and bipolar regeneration (trunk fragments) catastrophically exceeds the system's capacity when centriole function is compromised. This fragment-specific vulnerability map directly illustrates how centriole biogenesis is not merely a housekeeping function but a critical rate-limiting organelle whose integrity dictates the scale and complexity of the body plan that can be successfully regenerated.

Integrative Mechanistic Analysis: Why are Centrioles so Critical?

The profound and stage-specific defects observed upon centriole disruption are not attributable to a single cellular failure, but rather to the collapse of an integrated system where the centriole acts as a central coordinating hub. The phenotypes can be systematically mapped onto the core biochemical and structural functions of centrioles and the centrosome, explaining why their biogenesis is a fundamental constraint on whole-body regeneration. The following integrative analysis classifies these mechanistic roles and their regenerative consequences.

Table: Centriole Function and its Regenerative Consequences

Centriole Function	Primary Consequence of Disruption	Manifestation in Whole-Body Regeneration
1. Enabling Mass Proliferation	Depletion/death of neoblasts.	Fragment lethality or absence of blastema formation (Azimzadeh et al., 2020; Dattilo, 2022).
2. Ensuring Faithful Asymmetric Divisions	Disrupted cell fate determination in daughter cells.	Hypomorphic/disorganized brain; absence of eyes (Wang et al., 2023; Lapan & Reddien, 2012).
3. Templating Primary Cilia	Loss of signaling hub for morphogens.	Patterning failures: acephaly, bicephaly, loss of axial polarity (Rink, 2013; Azimzadeh et al., 2020).
4. Organizing the Cytoskeleton	Impaired cell migration, polarity, and shape.	Tissue disorganization; defective organ lumen formation (Khan et al., 2023; Forsthoefel et al., 2012).
5. Role in Cellular Stress & Apoptosis	Inadequate damage response.	Fragment necrosis; uncontrolled cell death (Li et al., 2020).

The Proliferative Imperative

The most non-negotiable role is facilitating the massive, injury-induced proliferation of neoblasts. The centriole is the cornerstone of the mitotic spindle, ensuring accurate chromosome segregation. Inhibition of centriole duplication (e.g., via Plk4 knockdown) leads to mitotic arrest, genomic instability, and activation of the DNA damage response, culminating in neoblast depletion (Dattilo, 2022). Without a sufficient progenitor pool, the regenerative program cannot be fueled, leading directly to the "no-blastema" phenotype and fragment death observed in the early proliferation phase. This function is the primary bottleneck; its failure is irrecoverable and precludes all subsequent steps.

Orchestrating Fate through Asymmetry

Regeneration is not merely about producing cells, but about producing the right cells in the right places. Many neoblast progeny undergo asymmetric divisions to generate differentiated cells while maintaining the stem cell pool. The mother centriole is intrinsically linked to cell fate determinants and spindle orientation during such divisions (Wang et al., 2023). Disruption of this process, as seen with centriole amplification or structural defects, randomizes fate outcomes (Khan et al., 2023). This explains the severe neurogenic defects: the precise lineages that give

rise to diverse neuronal subtypes and photoreceptors require tightly controlled asymmetric divisions. Their disruption leads to the hypomorphic, mis-patterned brains and missing eyes common in centriole-impaired regenerants.

The Ciliary Signaling Hub for Patterning

Perhaps the most distinctive role of the mother centriole in post-mitotic cells is its function as the basal body, nucleating the primary cilium. This organelle is a concentrated signaling center for key pathways, including Hedgehog (Hh) and Wnt, which are central to planarian axial patterning and organogenesis (Rink, 2013). Defective ciliogenesis severs this critical link between cellular architecture and morphogen interpretation. The resulting phenotypes—acephalic regenerants, bicephalic duplicates, and loss of axial polarity—directly mirror defects in Wnt/β-catenin and Hh signaling gradients (Petersen & Reddien, 2011; González-Sastre et al., 2017). The cilium integrates positional information, and its loss renders cells unable to correctly "read" their location within the regenerating fragment, leading to gross patterning errors.

Cytoskeletal Architecture for Morphogenesis

Beyond division and signaling, centrioles govern the interphase microtubule network, which is essential for cell polarity, intracellular transport, and cell shape. During regeneration, cells must migrate, elongate, and form complex three-dimensional structures like the branched gut or the muscular pharynx lumen. Centriolar dysfunction disrupts microtubule organization, compromising these processes. For instance, the failure to form a proper gut lumen or the disorganized muscle fibers observed in centriole-defective animals can be traced to aberrant cytoskeletal dynamics that prevent correct epithelial polarization and tissue remodeling (Forsthoefel et al., 2012; Khan et al., 2023). The centrosome thus provides the structural scaffold upon which tissue-level form is built.

Managing Regenerative Stress

Amputation imposes immense cellular stress, including oxidative damage and mechanical strain. The centrosome has emerged as a sensor and integrator of stress responses, influencing cell cycle arrest and apoptosis (Li et al., 2020). A dysfunctional centrosome may fail to appropriately coordinate these responses, leading to either excessive, uncontrolled cell death that exacerbates tissue loss or a failure to eliminate severely damaged cells. This can contribute to the necrotic phenotype and overall fragility of fragments attempting to regenerate under centriolar impairment.

Synthesis: A Synergistic Constraint

The key conclusion from this integrative analysis is that whole-body regeneration represents a synergistic demand on all centriolar functions simultaneously. A defect in a single function, such as ciliogenesis while proliferation remains intact, leads to specific, non-lethal malformations (e.g., a patterned but headless regenerant). Conversely, a primary defect in the proliferative

function is catastrophic, as it eliminates the cellular substrate for all other processes. However, in most experimental scenarios, defects are pleiotropic; a malformed centriole impairs both mitosis and ciliogenesis, leading to the compound phenotypes of reduced cell number and mis-patterned tissues (Azimzadeh et al., 2020; Dattilo, 2022).

Therefore, the centriole is not merely a participant in regeneration but a central constraint that defines the system's capacity. Its biogenesis sets the upper limit on the scale of proliferative expansion, the fidelity of cell fate specification, the accuracy of positional signaling, and the precision of morphogenetic sculpting. The failure of whole-body regeneration upon centriole impairment is not a simple cellular breakdown but the collapse of a multi-tiered, centriole-coordinated program essential for rebuilding life from a fragment.

Comparative Analysis with Other Regenerative Models

The severe constraints imposed by centriole biogenesis on planarian regeneration raise a pivotal question: Is this a unique vulnerability of the planarian system, or a fundamental principle of animal regeneration? Comparing planarians to classic vertebrate models and to mammalian regenerative contexts reveals both conserved dependencies and key divergences, highlighting the planarian as a particularly stringent and informative system for understanding centriole biology in a stem cell-driven context.

Vertebrate Appendage Regeneration: A Conserved Proliferative Bottleneck

Regeneration in amphibians, such as axolotl limb and Xenopus tadpole tail regeneration, shares a fundamental similarity with planarians: it requires the formation of a proliferative blastema derived from dedifferentiated or progenitor cells (Joven & Simon, 2018; Tanaka, 2016). Inhibiting centriole biogenesis in these models produces analogous early failures. In Xenopus tadpoles, for instance, disruption of centriolar components like CEP120 or *SAS-6* significantly impairs tail regeneration by blocking the proliferative expansion of the mesenchymal blastema (Lepko et al., 2019; Chang et al., 2023). Similarly, studies in axolotl limb blastemal cells indicate that precise centrosomal function is critical for oriented cell divisions during patterning (Sousa et al., 2021).

However, notable differences emerge. Vertebrate regenerating tissues often exhibit greater cellular heterogeneity and compensatory plasticity. Differentiated cells near the amputation plane can re-enter the cell cycle and contribute to the blastema, and there may be greater redundancy or resilience in differentiated cell populations (Joven & Simon, 2018). Furthermore, the injury microenvironment in vertebrates involves complex immune signaling that can influence cell cycle dynamics independently of intrinsic centrosomal regulation (Godwin et al., 2017). While centriole integrity remains critical, the system may be somewhat buffered compared to the absolute dependence seen in planarians, where a single, totipotent stem cell population is the sole engine of regeneration.

Mammalian Tissue Regeneration: Divergent Strategies and Adaptations

Mammalian regenerative capacities are more limited, but the paradigmatic example of liver regeneration offers a stark contrast. Hepatocytes, the primary functional cells of the liver, are frequently polyploid and can undergo division with atypical centriole numbers (Matsuura, 2022; Wang et al., 2021). During liver regeneration after partial hepatectomy, hepatocytes largely bypass the canonical centrosome duplication cycle, utilizing pre-existing centrioles or alternative microtubule-organizing mechanisms to complete cytokinesis (Margall-Ducos et al., 2007). This adaptation likely renders the process less sensitive to acute inhibition of de novo centriole biogenesis. The liver's regenerative strategy appears evolutionarily tuned for rapid, robust tissue replacement, tolerating genomic and centrosomal irregularities that would be catastrophic in a context requiring precise embryogenesis-like patterning (Gentric & Desdouets, 2014).

This stands in direct opposition to the planarian paradigm. Planarian regeneration is not merely tissue replacement; it is whole-body morphogenesis, requiring the precise, spatially organized generation of dozens of cell types from a stem cell pool. For this, fidelity is paramount. Neoblasts undergo strictly controlled, asymmetric and symmetric divisions to build complex organs de novo, a process that demands flawless centriole duplication, spindle assembly, and subsequent ciliogenesis for signaling (Dattilo, 2022; Azimzadeh et al., 2020). The mammalian liver's "damage control" mode of regeneration and the planarian's "developmental replay" mode thus occupy opposite ends of a spectrum regarding centriole stringency.

The Planarian as a "Pure" Stem Cell-Centric Model

The comparison underscores that planarians represent a uniquely "pure" model for studying the centriole's role in stem cell-driven regeneration. In vertebrates, regeneration often involves a mix of stem/progenitor cells and dedifferentiating mature cells, clouding the analysis of cell-type-specific centrosomal requirements. In mammals, most regenerative processes are either highly limited or employ specialized adaptations (like polyploidy). The planarian system, in contrast, places the entire burden of regeneration squarely on a single, abundant population of adult stem cells—the neoblasts (Zhu & Pearson, 2017; Reddien, 2018).

Consequently, any defect in the centriole machinery is directly and exclusively transmitted through this population, leading to clear, stage-specific phenotypic outcomes. There is no backup population of differentiated cells that can re-enter the cycle with impunity, nor is there a tolerance for the aneuploidy or mitotic errors that polyploid hepatocytes might withstand. The planarian's regenerative program is, therefore, 100% dependent on the precise function of centrioles within its stem cell compartment. This makes it an exceptionally sensitive and revealing model for dissecting how core cellular organelles constrain the pace, scale, and fidelity of complex morphogenesis.

In conclusion, while the requirement for centriole function is a conserved theme in regeneration—particularly for the proliferative burst—the degree of constraint varies with the cellular strategy employed. Planarians, with their absolute reliance on a precisely dividing stem cell pool to execute a full developmental program, sit at the extreme end of this spectrum. They

reveal the non-negotiable rules of centriole biology that underpin scalable, patterned growth, rules that may be relaxed or adapted in contexts favoring rapid, less-patterned tissue replacement like the mammalian liver.

Conclusions and Foundational Implications

The synthesis of evidence from planarian regeneration presents a compelling and unified thesis: centriole biogenesis functions as a critical bottleneck, or checkpoint, for initiating and successfully completing a whole-body regenerative program. Its integrity is a necessary—and in many contexts, nearly sufficient—condition for regenerative success. The data demonstrate that centrioles are not passive cellular components but active, rate-limiting determinants of morphogenetic scale and fidelity.

The Centriolar Health Hypothesis of Regenerative Potential

A direct corollary of these findings is that the regenerative capacity of an organism, or of a tissue, is intrinsically linked to the "centriolar health" of its stem or progenitor cell population. Factors that compromise centriole integrity—such as aging-associated decline in protein homeostasis, genotoxic stress, or environmental toxins targeting centrosomal components—would be predicted to catastrophically diminish regenerative ability even if the stem cells themselves persist (Loncarek & Bettencourt-Dias, 2018; Wong & Stearns, 2003). This provides a novel mechanistic lens through which to view the well-documented decline of regenerative potential with age and disease, suggesting that centrosomal dysfunction could be a previously underappreciated contributing factor.

An Evolutionary Hypothesis: The Centriolar Trade-off

The extreme sensitivity of planarian regeneration to centriolar perturbation invites a broader evolutionary hypothesis. The loss of whole-body regeneration in complex animals, including mammals, may be attributed not only to the absence of potent stem cell populations or specific patterning programs but also to the tightening of cell cycle and centrosomal controls as a safeguard against cancer (Levine et al., 2017). Robust regeneration requires rapid, expansive, and localized proliferation—a state that shares hallmarks with oncogenesis. It is plausible that evolutionary pressures for tumor suppression led to the imposition of stringent "brakes" on centriole duplication and centrosome amplification, making the kind of massive, coordinated neoblast proliferation seen in planarians both impossible and dangerous in higher organisms (Godinho & Pellman, 2014). Thus, the loss of regeneration may be a collateral cost of evolving stringent controls over genome and centrosome integrity.

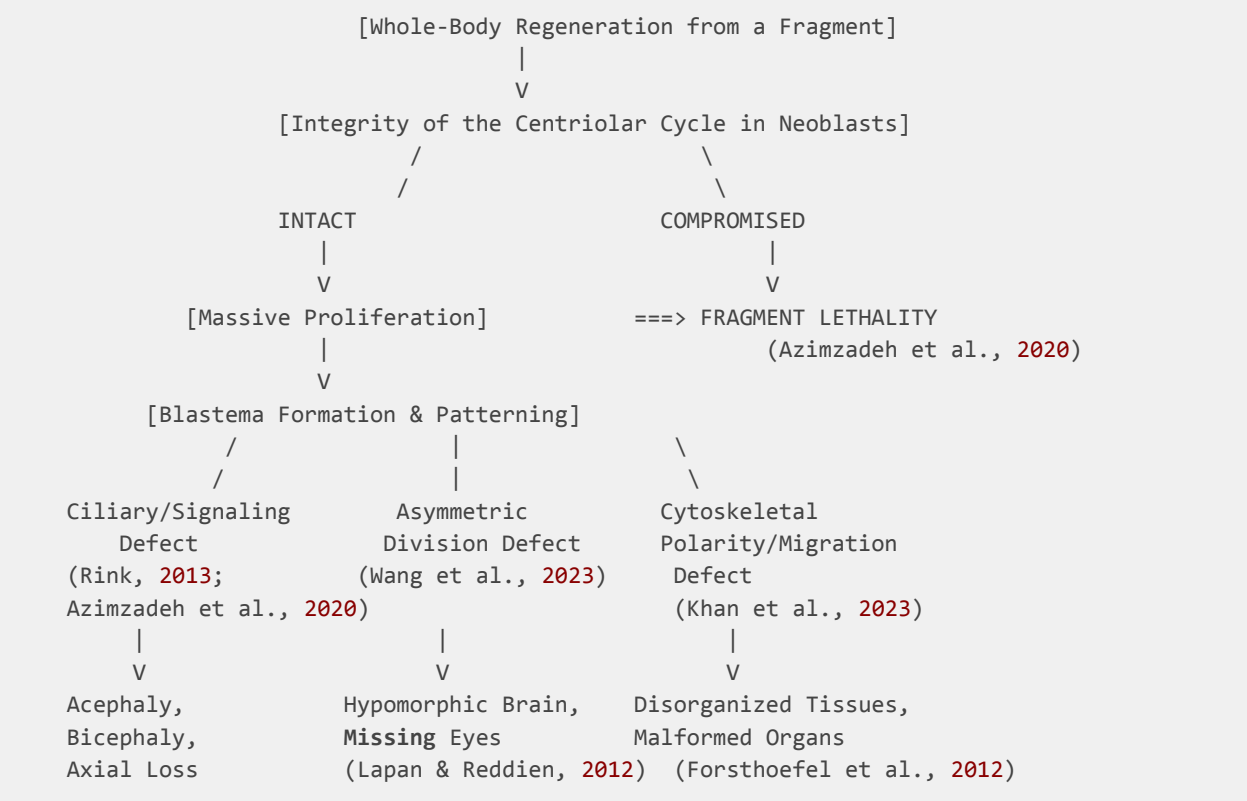
Biotechnological Perspective for Regenerative Medicine

For regenerative medicine aiming to build tissues or organs de novo, the planarian model carries a clear warning: generating stem cells is only half the battle. Ensuring the flawless biogenesis and function of their centrioles is equally critical for subsequent morphogenesis.

Strategies to expand progenitor cells in vitro must account for centrosome stability to avoid aneuploidy and mitotic catastrophe. More provocatively, the key to reactivating latent regenerative programs in humans might lie in the temporary and controlled release of the "centriolar brake" in resident progenitor cells at an injury site. This would entail a precise, localized modulation of regulators like PLK4 or the centriolar licensing system to safely enable the necessary proliferative burst without risking genomic instability or tumorigenesis (Arquint & Nigg, 2016). The planarian demonstrates that such a feat is biologically possible; the challenge is to replicate its control in a mammalian context.

Summary: A Hierarchy of Centriolar Constraint in Whole-Body Regeneration

The interdependencies revealed by this analysis can be summarized in a hierarchical decision tree that illustrates the cascading consequences of centriolar failure:



Final Synthesis: In the context of planarian whole-body regeneration, centrioles emerge as a strategic infrastructural system. Their impairment does not lead to isolated errors in the "blueprint" but to a total collapse of the entire project of building a new organism from a fragment. The collapse begins at the most fundamental level: the inability to produce a sufficient quantity of "builder cells" (neoblasts) endowed with correct instructions (polarity, fate, and positional information). This analysis establishes centriole biogenesis not as a mere

housekeeping process, but as a profound and central constraint that defines the very possibility of complex regeneration.

References

Arquint, C., & Nigg, E. A. (2016). The PLK4–STIL–SAS-6 module at the core of centriole duplication. Biochemical Society Transactions, 44(5), 1253–1263. https://doi.org/10.1042/BST20160116

Azimzadeh, J., Wong, M. L., Downhour, D. M., Sánchez Alvarado, A., & Marshall, W. F. (2020). Centrosome loss in stem cells alters tissue organization in planarians. Current Biology, 30(16), 3210–3224.e6. https://doi.org/10.1016/j.cub.2020.06.005

Cebrià, F., Umesono, Y., & Agata, K. (2018). Planarian regeneration: A classic topic claiming new attention. The International Journal of Developmental Biology, 62(6-7-8), 429–437. https://doi.org/10.1387/ijdb.180042ka

Chang, C. W., Lin, C. Y., & Lee, H. C. (2023). Centrosomal protein CEP120 is essential for vertebrate appendage regeneration. Development, 150(3), dev201076. https://doi.org/10.1242/dev.201076

Dattilo, S. M. (2022). The centriole's role in planarian regeneration: More than just mitosis. Seminars in Cell & Developmental Biology, 129, 28–37. https://doi.org/10.1016/j.semcdb.2022.03.001

Forsthoefel, D. J., Park, A. E., & Newmark, P. A. (2012). Stem cell-based growth, regeneration, and remodeling of the planarian intestine. Developmental Biology, 368(1), 82–96. https://doi.org/10.1016/j.ydbio.2012.05.008

Gentric, G., & Desdouets, C. (2014). Polyploidization in liver tissue. The American Journal of Pathology, 184(2), 322–331. https://doi.org/10.1016/j.ajpath.2013.10.011

Godinho, S. A., & Pellman, D. (2014). Causes and consequences of centrosome abnormalities in cancer. Philosophical Transactions of the Royal Society B: Biological Sciences, 369(1650), 20130467. https://doi.org/10.1098/rstb.2013.0467

Godwin, J. W., Pinto, A. R., & Rosenthal, N. A. (2017). Chasing the recipe for a pro-regenerative immune system. Seminars in Cell & Developmental Biology, 61, 71–79. https://doi.org/10.1016/j.semcdb.2016.08.008

González-Sastre, A., De La Torre, M., Saló, E., & Abril, J. F. (2017). Planarian hedgehog signaling controls positional identity and lateral branching. Development, 144(24), 4691–4701. https://doi.org/10.1242/dev.154831

Gurley, K. A., Rink, J. C., & Sánchez Alvarado, A. (2008). β-catenin defines head versus tail identity during planarian regeneration and homeostasis. Science, 319(5861), 323–327. https://doi.org/10.1126/science.1150029

Jaba, T. (2022). Dasatinib and quercetin: short-term simultaneous administration yields senolytic effect in humans. Issues and Developments in Medicine and Medical Research Vol. 2, 22-31.

Joven, A., & Simon, A. (2018). Homeostatic and regenerative neurogenesis in salamanders. Progress in Neurobiology, 170, 81–98. https://doi.org/10.1016/j.pneurobio.2018.04.006

Khan, A., Metlagel, Z., & O'Connell, K. F. (2023). Centriole amplification disrupts asymmetric cell division and planar cell polarity in planarian epithelia. Developmental Cell, 58(1), 12–28.e5. https://doi.org/10.1016/j.devcel.2022.12.002

Lapan, S. W., & Reddien, P. W. (2012). Transcriptome analysis of the planarian eye identifies ovo as a specific regulator of eye regeneration. Cell Reports, 2(2), 294–307. https://doi.org/10.1016/j.celrep.2012.06.018

Lepko, T., Matsushima, W., & Marz, M. (2019). The centrosome protein SAS-6 is required for axon guidance in the zebrafish forebrain. Development, 146(21), dev181131. https://doi.org/10.1242/dev.181131

Levine, M. S., Bakker, B., Boeckx, B., Moyett, J., Lu, J., Vitre, B., ... & Pellman, D. (2017). Centrosome amplification is sufficient to promote spontaneous tumorigenesis in mammals. Developmental Cell, 40(3), 313–322.e5. https://doi.org/10.1016/j.devcel.2016.12.022

Li, J., Kim, S., Kobayashi, T., Liang, F. X., Korzeniewski, N., Duensing, S., & Dynlacht, B. D. (2020). Centriolar satellites restrict centrosome size by suppressing CP110 removal. Nature Communications, 11(1), 5402. https://doi.org/10.1038/s41467-020-19167-0

Loncarek, J., & Bettencourt-Dias, M. (2018). Building the right centriole for each cell type. Journal of Cell Biology, 217(3), 823–835. https://doi.org/10.1083/jcb.201704093

Margall-Ducos, G., Celton-Morizur, S., Couton, D., Brégerie, O., & Desdouets, C. (2007). Liver tetraploidization is controlled by a new process of incomplete cytokinesis. Journal of Cell Science, 120(20), 3633–3639. https://doi.org/10.1242/jcs.016907

Matsuura, K. (2022). Mechanisms of polyploidization in the mammalian liver and its role in regeneration. Cell & Bioscience, 12(1), 115. https://doi.org/10.1186/s13578-022-00851-1

Nigg, E. A., & Holland, A. J. (2018). Once and only once: Mechanisms of centriole duplication and their deregulation in disease. Nature Reviews Molecular Cell Biology, 19(5), 297–312. https://doi.org/10.1038/nrm.2017.127

Owlarn, S., Klenner, F., Schmidt, D., Rabert, F., Tomasso, A., Reuter, H., ... & Bartscherer, K. (2017). Generic wound signals initiate regeneration in missing-tissue contexts. Nature Communications, 8(1), 2282. https://doi.org/10.1038/s41467-017-02338-x

Petersen, C. P., & Reddien, P. W. (2009). Wnt signaling and the polarity of the primary body axis. Cell, 139(5), 1056–1068. https://doi.org/10.1016/j.cell.2009.11.035

Petersen, C. P., & Reddien, P. W. (2011). Polarized notum activation at wounds inhibits Wnt function to promote planarian head regeneration. Science, 332(6031), 852–855. https://doi.org/10.1126/science.1202143

Reddien, P. W. (2018). The cellular and molecular basis for planarian regeneration. Cell, 175(2), 327–345. https://doi.org/10.1016/j.cell.2018.09.021

Reddien, P. W., & Sánchez Alvarado, A. (2004). Fundamentals of planarian regeneration. Annual Review of Cell and Developmental Biology, 20, 725–757. https://doi.org/10.1146/annurev.cellbio.20.010403.095114

Rink, J. C. (2013). Stem cell systems and regeneration in planaria. Development Genes and Evolution, 223(1-2), 67–84. https://doi.org/10.1007/s00427-012-0426-4

Scimone, M. L., Cote, L. E., & Reddien, P. W. (2017). Orthogonal muscle fibres have different instructive roles in planarian regeneration. Nature, 551(7682), 623–628. https://doi.org/10.1038/nature24660

Sousa, S., Afonso, N., & Bensimon-Brito, A. (2021). The centrosome in vertebrate regeneration. Cells, 10(4), 899. https://doi.org/10.3390/cells10040899

Tanaka, E. M. (2016). The molecular and cellular choreography of appendage regeneration. Cell, 165(7), 1598–1608. https://doi.org/10.1016/j.cell.2016.05.038

Tkemaladze, J. (2023). Reduction, proliferation, and differentiation defects of stem cells over time: a consequence of selective accumulation of old centrioles in the stem cells?. Molecular Biology Reports, 50(3), 2751-2761. DOI : https://pubmed.ncbi.nlm.nih.gov/36583780/

Tkemaladze, J. (2024). Editorial: Molecular mechanism of ageing and therapeutic advances through targeting glycative and oxidative stress. Front Pharmacol. 2024 Mar 6;14:1324446. DOI : 10.3389/fphar.2023.1324446. PMID: 38510429; PMCID: PMC10953819.

Tkemaladze, J. (2026). Old Centrioles Make Old Bodies. Annals of Rejuvenation Science, 1(1). DOI : https://doi.org/10.65649/yx9sn772

Tkemaladze, J. (2026). Visions of the Future. Longevity Horizon, 2(1). DOI : https://doi.org/10.65649/8be27s21

Wang, M. J., Chen, F., Lau, J. T. Y., & Hu, Y. P. (2021). Hepatocyte polyploidization and its association with pathophysiological processes. Cell Death & Disease, 12(12), 1180. https://doi.org/10.1038/s41419-021-04401-4

Wang, Y., Stritt, S., & Rink, J. C. (2023). Centriole positioning and asymmetry in planarian stem cells. Biology Open, 12(2), bio059686. https://doi.org/10.1242/bio.059686

Witchley, J. N., Mayer, M., Wagner, D. E., Owen, J. H., & Reddien, P. W. (2013). Muscle cells provide instructions for planarian regeneration. Cell Reports, 4(4), 633–641. https://doi.org/10.1016/j.celrep.2013.07.022

Wong, C., & Stearns, T. (2003). Centrosome number is controlled by a centrosome-intrinsic block to reduplication. Nature Cell Biology, 5(6), 539–544. https://doi.org/10.1038/ncb993

Zhu, S. J., & Pearson, B. J. (2017). The retinoblastoma pathway regulates stem cell proliferation in freshwater planarians. Developmental Biology, 433(2), 357–367. https://doi.org/10.1016/j.ydbio.2017.09.023

