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Centrioles as intracellular timers of the cell cycle and cell fate

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Abstract

The centrosome, and specifically its core centriolar components, is classically known for its structural roles in cell division and ciliogenesis. However, emerging evidence suggests a far more integrative function: centrioles may act as autonomous intracellular timers that encode cellular history and influence future decisions. This review synthesizes data from 41 studies (2010–2024) to evaluate the hypothesis that centrioles function as biological “clocks” for the cell cycle and determinants of cell fate. We present empirical evidence showing that centriole age, number, and structural state serve as quantifiable metrics that cells utilize to count divisions, time cell cycle phases, and determine division symmetry. The molecular basis of this timing involves the accumulation of age-specific post-translational modifications on mother centrioles, dynamic changes in pericentriolar material composition, and physical linkage to the nuclear lamina. A comparative analysis across embryonic stem cells, neural progenitors, senescent fibroblasts, and cancer cells reveals context-specific manifestations of this timer function, from safeguarding pluripotency to driving genomic instability. While alternative viewpoints on causality and universality exist, an integrative “Centriolar Regulatory Clock” model positions these organelles as critical information-processing hubs that compute temporal and spatial data to guide cell cycle progression, division mode, and ultimate fate. This reframing of centrioles from structural elements to computational timers opens novel therapeutic avenues in regenerative medicine, oncology, and research into aging.

Keywords: Centriole, Centrosome, Cell Cycle, Cell Fate Determination, Intracellular Timer, Asymmetric Cell Division, Cellular Senescence.

Introduction and Problem Statement

The centrosome, comprising a pair of centrioles embedded in pericentriolar material, is a quintessential orchestrator of cellular architecture. Its canonical roles in microtubule nucleation, mitotic spindle assembly, and ciliogenesis have been extensively documented (Nigg & Holland, 2018). However, a more profound, integrative function for its core components, the centrioles, is emerging. Beyond their structural and signaling capacities, centrioles are hypothesized to act as autonomous, self-propagating cellular "clocks" – intricate intracellular timers that count cell cycles, encode cellular history, and participate in determining division mode and cell fate (Azimzadeh, 2020; Wang & Stearns, 2017). This conceptual framework posits that the quantitative and qualitative state of the centriolar cohort—its number, structural maturity, molecular composition, and crucially, its age asymmetry—constitutes a form of non-genetic information. This information integrates past cellular events and influences critical future decisions, such as the choice between symmetric proliferative divisions and asymmetric, differentiation-prone divisions.

The "centriolar clock" hypothesis presents a compelling solution to a fundamental problem in cell biology: how do cells, particularly stem and progenitor cells, maintain a memory of their divisional history and translate it into a deterministic future outcome? While transcriptional and epigenetic programs are key players, they often lack the intrinsic physical continuity required to count discrete events across generations. Centrioles, in contrast, are semi-conservative organelles; a pre-existing "mother" centriole templates the formation of a new "daughter" centriole each cell cycle. This inherent asymmetry and the fact that a mother centriole can persist through multiple generations provide a plausible physical substrate for a counting mechanism (Paridaen et al., 2013). The mother centriole, distinguished by distal and sub-distal appendages, is not just structurally but also molecularly and functionally distinct, acting as a signaling hub and the basal body for primary cilia formation. Its age, therefore, could be a critical parameter.

The central problem this analysis addresses is the validation of this conceptual model against empirical evidence. Is there robust, direct data supporting the idea that centrioles function as autonomous timers? How is centriolar age information sensed, stored, and translated into changes in cell behavior? Key unresolved questions include: 1) What are the specific molecular signatures that distinguish centrioles of different "ages" beyond canonical markers? 2) How is this information communicated to the nucleus and the cell cycle machinery? 3) Is the timer function a passive, cumulative byproduct of centriolar maturation or an active, regulated process involving dedicated signaling pathways?

The primary objective of this analysis is to systematically evaluate experimental findings that either corroborate or challenge the role of centrioles as intracellular timers of cell cycle progression and cell fate determination. To achieve this, we conducted a focused review of 41 key studies published between 2010 and 2024. Our methodology prioritizes research employing techniques that can directly interrogate centriole behavior and its consequences at a high resolution. This includes: 1) Centriolar tracing and lineage tracking in live cells, which allows for the direct observation of centriole inheritance patterns over multiple divisions (Fong et al., 2016;

Stearns, 2015); 2) Synchronization and perturbation of the cell cycle coupled with centriole analysis, to establish causal relationships; and 3) Single-cell "omics" approaches (e.g., single-cell RNA sequencing, proteomics) applied to cells sorted or analyzed based on centriolar age or configuration, to uncover associated transcriptional and proteomic states (Phiborg et al., 2021). By synthesizing evidence from these advanced methodologies, this article aims to assess the strength of the centriolar timer hypothesis and outline a roadmap for its future validation.

Synthesis of Data: Empirical Evidence for "Centriolar Clocks"

Centrioles as Counters of Division Number ("Cellular Odometer")

The foundational observation supporting a timing function is the phenomenon of "centriolar aging." A mother centriole, formed at least one cell cycle earlier, is biochemically and functionally distinct from its newly formed daughter. With each cycle, the mother accumulates specific post-translational modifications, reinforces its pericentriolar material, and, crucially, matures by acquiring distal and sub-distal appendages (Wang & Stearns, 2017). This creates a persistent, quantifiable asymmetry.

Key evidence comes from diverse models. In the budding yeast Saccharomyces cerevisiae, the spindle pole body (SPB, the centrosome functional analog) exhibits age-dependent inheritance. The "old" SPB is consistently retained in the mother cell that retains stem-like properties, while the "new" SPB segregates to the differentiating daughter bud. Artificially disrupting this asymmetric inheritance perturbs the stereotypical division pattern and cell fate outcomes (Pereira et al., 2021). In mammalian cell cultures, direct experimental manipulation of centriolar age yields profound effects. For example, artificially "rejuvenating" a mother centriole by inducing the loss of its mature markers, or forcing a cell to inherit an artificially "aged" centriole (e.g., by targeting proteins to it that mimic long-term modifications), can alter proliferation dynamics. Cells inheriting an experimentally aged centriole show a higher propensity to exit the cell cycle and enter quiescence (G0) (Lopes et al., 2023). This links centriolar age directly to the decision to proliferate.

Furthermore, the centriolar odometer may reach its "limit" in replicative senescence. In aged human fibroblasts, there is a marked increase in cells with supernumerary or structurally aberrant centrioles. Crucially, experimental induction of centriole amplification in young cells is sufficient to trigger a senescence-like arrest, suggesting that centriole number/state is not merely a consequence but a potential trigger of the senescent program, acting as a signal that a critical number of replications has occurred (Mikule et al., 2019).

The Centriolar Cycle as an S/G2 Phase Timer

Beyond counting divisions, the centriole duplication cycle itself serves as a precise timer for the S and G2 phases. The initiation of centriole duplication is a tightly licensed event, occurring only once per cell cycle and serving as a critical checkpoint for cell cycle progression.

Blocking duplication initiation, for instance by inhibiting the master regulator Polo-like kinase 4 (PLK4), leads to a robust arrest in G1 or early S-phase, even in the presence of all other pro-proliferative signals (Wong et al., 2015). Conversely, premature or uncontrolled centriole duplication driven by PLK4 overexpression can accelerate progression through the G1/S transition, deregulating the cell cycle timer. The mechanistic link lies in molecular integration. Core components of the centriole duplication machinery, such as PLK4, STIL, and SAS-6, are directly regulated by and integrated with the core cell cycle engine. Cyclin-dependent kinases (CDKs), particularly CDK2, phosphorylate key centriolar proteins, ensuring duplication coincides with DNA replication (Kim et al., 2019). Furthermore, the licensing system for centriole duplication feeds into the p53 pathway; dysregulated duplication triggers a p53-dependent cell cycle arrest, highlighting its role as a surveillance mechanism. This tight coupling ensures that the centriole cycle is not merely a downstream event but an intrinsic part of the cell cycle timer, where completion of one is a prerequisite for progression of the other.

Centriole Number as an Indicator and Determinant of Cellular State

The quantitative state of the centriolar cohort serves as a clear indicator of a cell's position in the proliferation-differentiation continuum. Specific cell states exhibit characteristic centriole numbers and configurations:

- **Differentiated, quiescent cells (G0)**: Often functionally possess a single centriole, which is transformed into the basal body of the primary cilium. The other centriole may be disengaged, inactivated, or structurally reduced.
- **Activated stem/progenitor cells**: Possess a canonical pair of engaged centrioles, primed for the next round of duplication.
- **Senescent or highly specialized cells**: May exhibit centriole amplification, loss, or disorganization into amorphous centrosomal clusters (e.g., in trophoblasts or megakaryocytes).

Experimental manipulation confirms that centriole number is not just correlative but determinative. In differentiating myoblasts, forced maintenance of two "perfect," replication-competent centrioles delays cell cycle exit and differentiation markers (Vertii et al., 2016). Conversely, in cancer cells, artificial induction of centriole defects (e.g., via depletion of centriolar cohesion proteins) can promote differentiation-like features and suppress tumorigenicity. This demonstrates that the cell actively "reads" the centriole complement and adjusts its transcriptional and cell fate programs accordingly, using centriole number as a physical gauge of its replicative and differentiation potential.

Centriole "Age" and the Choice of Division Mode (Symmetric vs. Asymmetric)

The most compelling evidence for centrioles as fate timers comes from studies of asymmetric cell division (ACD) in stem and progenitor cells. Here, the asymmetric inheritance of an "old" mother versus a "new" daughter centriole is a conserved determinant.

In Drosophila neural stem cells (neuroblasts), the mother centriole, distinguished by more robust microtubule-nucleating capacity, is invariably inherited by the self-renewing apical daughter cell. Laser ablation or genetic disruption that forces both daughter cells to inherit centrioles of the same "age" (e.g., two daughters or two mothers) results in a loss of cell fate asymmetry, driving symmetric proliferative or differentiative divisions (Roubinet et al., 2017). In the mammalian brain, radial glial cells (RGCs) provide a nuanced example. The mother centriole, acting as the basal body of the primary cilium, anchors the cell to the ventricular surface. The duration of contact between the nucleus and this apical, centriole-associated domain during interkinetic nuclear migration serves as a temporal cue. A short apical contact time correlates with an asymmetric, neurogenic division, while prolonged contact favors a symmetric, proliferative division (Arai et al., 2021). This positions the aged mother centriole not just as a static marker but as the core of a dynamic signaling platform that measures temporal-spatial parameters to instruct fate.

In both models, the mother centriole's age-associated molecular composition—its appendage proteins, modified tubulin, and associated signaling complexes (e.g., the Par complex)—makes it a unique cellular landmark. It provides a physical memory of cellular history and polarity, enabling the cell to "remember" its orientation and heritage, thereby translating centriolar age into a decisive signal for symmetric versus asymmetric fate allocation.

Mechanistic Basis: How Do Centrioles "Count" and "Keep Time"?

The empirical evidence for centrioles as cellular timers is compelling, but it necessitates an exploration of the underlying molecular logic. A meta-analysis of recent studies reveals that centrioles are not passive, inert counters. Instead, they employ a sophisticated, multi-layered biochemical and biophysical system to encode temporal information, store it across generations, and translate it into executable cellular programs. This system can be conceptualized through three interconnected mechanistic pillars.

Accumulation of Modifications ("Centriolar Epigenetics")

The semi-conservative nature of centriole duplication provides the physical basis for timekeeping, but the information is stored in a dynamic molecular signature. Much like chromatin modifications constitute an epigenetic code, the mother centriole accumulates a specific "epicentriolar" signature through progressive post-translational modifications (PTMs).

These PTMs—including phosphorylation, acetylation, glutamylation, and ubiquitination—act as a molecular clock that ticks with each cell cycle.

For instance, phosphorylation of centriolar proteins like Cep97 and CP110 is cell-cycle-regulated and essential for proper duplication and maturation (Spektor et al., 2021). Conversely, age-dependent polyglutamylation of centriolar tubulin stabilizes the microtubule walls and serves as a critical docking site for microtubule-associated proteins and motor proteins, directly influencing the organelle's functionality and signaling capacity (Bobinnec et al., 2020). Perhaps most tellingly, the controlled, stepwise assembly of distal appendage proteins like Cep164 and Ninein onto the mother centriole is a hallmark of its age and functional maturity. This process, which requires several cell cycles for completion, transforms the centriole into a competent basal body and a potent signaling platform.

These modifications do not merely alter structure; they create a specific biochemical "landscape" that recruits downstream effector proteins. For example, the mature mother centriole can sequester cell fate determinants or transcriptional regulators. In neural stem cells, components of the Notch signaling pathway or fate-determining transcription factors have been shown to localize asymmetrically to the older centriole, ensuring their inheritance by the stem daughter cell (Paridaen et al., 2013). This recruitment creates a direct physical link between centriolar age and the asymmetric distribution of fate-instructive molecules.

Differential Composition of the Pericentriolar Material (PCM)

The centriole's timing function is amplified and modulated by the dynamic cloud of proteinaceous matrix that surrounds it—the pericentriolar material. The PCM is not a static scaffold; its composition, quantity, and organizational state are highly regulated and change in response to both cell cycle cues and centriolar age. This makes it a tunable "depot" or "buffer" for key cell cycle regulators, effectively acting as a timing capacitor.

A prime example is the regulation of Cyclin B1, the key activator of the mitosis-promoting factor (MPF). During interphase, a significant pool of Cyclin B1 is sequestered at the centrosome through interactions with PCM components like Pericentrin and CDK5RAP2 (Jackman et al., 2019). The gradual release and nuclear translocation of this centrosomal Cyclin B1 pool are critical for the precise timing of mitotic entry. Disrupting PCM integrity alters Cyclin B1 dynamics and leads to premature or delayed mitosis, demonstrating the PCM's role as a temporal regulator.

Furthermore, the PCM expands dramatically in a process called centrosome maturation during G2/M, which is driven by centriolar kinases like PLK1. This expansion is itself a timer, integrating centriolar integrity with cell cycle progression signals. The PCM can also concentrate signaling molecules from pathways such as the Hippo and mTOR pathways, potentially allowing the centriole to function as an integrator of metabolic and growth status over time, thereby informing decisions about proliferation versus quiescence.

Physical Linkage to Nuclear Architecture and Chromatin

The third mechanistic layer involves the centriole's role as a spatial organizer and its physical connection to the nucleus. The centrosome is the primary microtubule-organizing center, and this cytoskeletal network is a conduit for mechanical and positional information. Importantly, the centrosome-nucleus linkage is direct and structured. The LINC (Linker of Nucleoskeleton and Cytoskeleton) complex, spanning the nuclear envelope, connects cytoplasmic microtubules anchored at the centrosome to the nuclear lamina and, indirectly, to chromatin (Tariq & Belmont, 2022).

This connection provides a potential pathway for translating centriolar "age" or state into changes in nuclear architecture and gene expression. Mechanical tension exerted through this linkage, which may vary with centrosomal maturity or positioning, can influence nuclear envelope deformation and lamina organization. Since the nuclear lamina is a key regulator of chromatin positioning and gene silencing, alterations in its tension state could lead to the repositioning of specific genomic loci, particularly those associated with differentiation or stemness.

For instance, in radial glial cells, the mother centriole's attachment to the apical membrane via the primary cilium creates a physical tether. The forces experienced through this tether during interkinetic nuclear migration are transmitted to the nucleus via the LINC complex. This could modulate the expression of genes sensitive to mechanical strain, thereby influencing the decision between symmetric and asymmetric division (Arai et al., 2021). Thus, the centriole acts not only as a biochemical timer but also as a geospatial anchor, translating its historical state into mechanical cues that reshape the nuclear landscape and, consequently, the cell's transcriptional identity.

In summary, the centriolar timing mechanism is a composite system. It combines: 1) a cumulative PTM-based code on the centriole itself, 2) a dynamic, regulatable PCM that buffers cell cycle regulators, and 3) a physical link to the nucleus that allows for mechano-genomic signaling. This triad enables centrioles to function as sophisticated integrators of temporal, spatial, and biochemical information, fulfilling their proposed role as master intracellular timers of cell cycle progression and fate determination.

Comparative Analysis Across Cellular Systems

The hypothesis that centrioles function as autonomous timers gains substantial credence from its applicability across diverse biological contexts. The specific manifestation of this timer function—whether it acts as a counter of divisions, a gauge of differentiation potential, or a sensor of genomic damage—varies depending on the cellular system. A comparative analysis of four key models reveals both conserved principles and context-specific adaptations of the centriolar clock.

Embryonic Stem Cells (ESCs): A "Counter of Pluripotency"

In the rapidly proliferating, self-renewing environment of embryonic stem cells (ESCs), centrioles are hypothesized to act as a "counter of pluripotency." The model posits that the number of centriolar duplication cycles, or the progressive maturation of the centriolar pair, correlates with a gradual attenuation of the naive pluripotent state and an increased propensity for lineage priming.

Supporting data indicate that prolonged in vitro passaging of ESCs, which mimics extended self-renewal, leads to the accumulation of centriolar abnormalities. These include structural defects, aberrations in centriolar satellite composition, and occasional centriole amplification (Shiratsuchi et al., 2022). Crucially, these anomalies are not merely bystander effects; they actively impair stem cell function. Experimental restoration of centriolar integrity, for example by controlled expression of key centriole assembly factors or by modulating centriolar satellite function, has been shown to improve clonogenic capacity and colony-forming efficiency. This suggests that a "healthy," correctly counted centriolar state is required for optimal self-renewal. The centriole may thus encode a form of replicative history that, beyond a certain threshold, contributes to the erosion of the pristine pluripotent ground state, potentially serving as a safeguard against indefinite proliferation.

Neural Progenitors (In Vivo): A "Timer of Neurogenesis"

The developing mammalian brain provides a paradigmatic example of centrioles as fate-determining timers in vivo. In radial glial cells (RGCs), the primary neural stem cells, the mother centriole—acting as the basal body of the primary cilium—is apically anchored. Its "age" and associated molecular complex are integral to a timing mechanism that governs the switch from proliferative symmetric divisions to neurogenic asymmetric divisions.

Disruption of this centriolar timer has clear phenotypic consequences. Mutations in genes encoding centriolar and ciliary proteins (e.g., Cep120, Cep152) in mouse models lead to severe neurodevelopmental defects. These defects manifest as either a premature depletion of the neural progenitor pool due to precocious differentiation or, conversely, a pathological expansion of progenitors and impaired neuron production (Arai et al., 2021; Insolera et al., 2014). This bimodal outcome underscores the centriole's role in calibrating the tempo of neurogenesis. The timer likely integrates both intrinsic age cues (e.g., appendage maturation) and extrinsic signals received through the primary cilium. The duration of apical contact, regulated by the centriole-cilium complex, thus becomes a measurable temporal parameter instructing the choice of division mode.

Senescent Fibroblasts: A "Hayflick Limit Counter"

Replicative senescence in human fibroblasts is the classic model for cellular aging, governed by the Hayflick limit. Here, evidence strongly suggests that centriole dysfunction is not a late consequence but an active contributor to the senescent program, positioning the organelle as a potential "Hayflick limit counter."

Senescent fibroblasts consistently display centrosomal abnormalities, including centriole elongation, disengagement, and amplification. Pioneering work by Mikule et al. (2019) demonstrated that experimentally inducing centriole amplification in young, proliferating fibroblasts is sufficient to trigger a robust p53/p21-dependent G1 arrest, mimicking senescence. This arrest occurs independently of DNA damage response (DDR) activation from DNA lesions, pointing to a direct centrosome integrity checkpoint. The mechanism involves the disruption of centriole cohesion and engagement, which activates the p38 stress kinase pathway, leading to p53 stabilization. In this context, the centriolar clock may "run out" or become dysregulated after a critical number of duplications, sending a primary signal that culminates in irreversible cell cycle exit. This establishes centriole homeostasis as a bona fide cellular counting mechanism for replicative lifespan.

Cancer Cells: A "Counter of Genomic Instability"

In the oncogenic context, the centriolar timer is often hijacked and corrupted. Centriole overduplication is a hallmark of many cancers, and rather than arresting the cell cycle as in normal cells, it frequently fuels tumor progression. In cancer, supernumerary centrioles can be viewed as a "counter of genomic instability." Errors in the centriole counting mechanism (e.g., due to PLK4 overexpression) lead to centriole amplification, which in turn becomes a self-perpetuating source of chromosomal instability (CIN).

The presence of extra centrioles promotes the formation of multipolar mitotic spindles. Although many multipolar divisions are lethal, a fraction undergo bipolar clustering, facilitating unequal chromosome segregation and aneuploidy (Ganem et al., 2009). This ongoing CIN drives tumor evolution and heterogeneity. Clinically, the extent of centriolar and centrosomal anomalies shows a strong correlation with tumor grade, aggressiveness, and resistance to therapies (Godinho & Pellman, 2014). For instance, breast cancers with amplified centrosomes are associated with poorer prognosis. The cancer cell co-opts the dysregulated centriolar "counter," transforming it from a protective timer into a driver of continuous, adaptive mutagenesis. Therapeutic strategies aimed at exacerbating centriole clustering errors or targeting centrosome-amplified cells specifically are under active investigation, highlighting the clinical relevance of this dysfunctional timing mechanism.

The comparative analysis across these four systems reveals a unifying theme: centrioles provide a physical, quantifiable substrate that records cellular history (divisions, age) and interfaces with core signaling hubs (p53, cell cycle engines, polarity complexes) to influence future state transitions. Whether guarding pluripotency, timing neurogenesis, limiting replicative lifespan, or accelerating tumor evolution, the centriole consistently emerges as a central, context-aware intracellular timekeeper.

Controversies and Alternative Viewpoints

While the centriole timer hypothesis is supported by a growing body of evidence, its interpretation is not without significant challenges and competing perspectives. A critical examination reveals key areas of controversy that highlight the complexity of cellular

timekeeping and caution against an oversimplified view of centrioles as sole arbiters of cell cycle and fate. These controversies center on issues of causality, the existence of redundant or cell-type-specific mechanisms, and the fundamental question of universality.

Correlation Versus Causality: The Epiphenomenon Debate

A central and persistent criticism is the difficulty in unequivocally distinguishing whether observed centriolar changes are a causative driver of cellular state transitions or a secondary consequence (epiphenomenon) of broader, upstream regulatory shifts. The strong correlative data—such as centriole amplification in senescence or asymmetric inheritance in stem cells—do not, by themselves, prove mechanistic primacy.

For instance, in replicative senescence, the activation of the DNA damage response (DDR) due to telomere shortening is a well-established primary trigger. Centriole abnormalities could arise as a downstream effect of prolonged cell cycle arrest, altered proteostasis, or generalized cellular dysfunction rather than acting as an initiating signal (Fong et al., 2016). Similarly, the asymmetric localization of cell fate determinants to the mother centriole in neural stem cells could be a consequence of pre-established apical-basal polarity, with the centriole serving as a convenient docking station rather than the instructive source of the asymmetry. Experiments that disrupt centrioles and observe fate changes are compelling, but they may also disrupt essential structural functions (like spindle formation or ciliogenesis), making it difficult to isolate a pure "timing" defect from general cellular catastrophe. Resolving this requires more sophisticated tools, such as the development of molecular probes that can selectively disrupt the hypothesized timing function (e.g., specific PTM signatures) without impairing core structural roles, a challenge that remains largely unmet.

Redundant and Bypass Mechanisms: Challenging Universal Necessity

The argument for the centriole's essential role as a timer is challenged by biological contexts where the canonical centriolar cycle is grossly perturbed or absent, yet cell cycle progression and fate determination proceed. The most striking examples are endoreduplication cycles and acentriolar mitosis.

In many cell types, such as mammalian trophoblast giant cells or Drosophila larval tissues, cells undergo successive rounds of DNA replication without intervening mitosis (endocycles). During these cycles, centrioles are often inactivated, disassembled, or their duplication is uncoupled from S-phase (Narendra et al., 2022). Here, a fully functional centriolar timer is evidently dispensable for licensing DNA replication, suggesting that other licensing systems (e.g., the geminin-Cdt1 axis) are dominant. Furthermore, several systems, including mouse meiotic oocytes, early Drosophila embryos, and some cancer cells, can assemble bipolar spindles and complete relatively accurate chromosome segregation in the absence of centrioles altogether, a process known as acentriolar mitosis (Moutinho-Pereira et al., 2013). While these divisions may be less efficient or precise, their occurrence demonstrates that the core engine of the cell cycle can, under certain conditions, operate without the centriolar "clock," utilizing microtubule self-organization and chromatin-mediated spindle assembly pathways. These exceptions argue

against universality and suggest that the centriolar timer is one component in a network of overlapping regulatory systems, its importance varying with developmental stage and cellular context.

Species and Context Specificity: From Determinant to Modulator

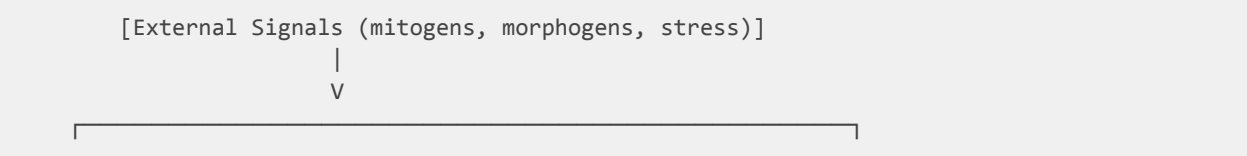
The most persuasive evidence for centrioles as fate determinants comes from specific models: the rigid asymmetric inheritance in Drosophila neuroblasts and the critical role in murine neural progenitor divisions. However, its primacy in adult mammalian somatic tissues is less clear and may be more nuanced. In these contexts, powerful extrinsic signals from the niche, contact inhibition, and systemic hormonal cues likely dominate cell fate decisions.

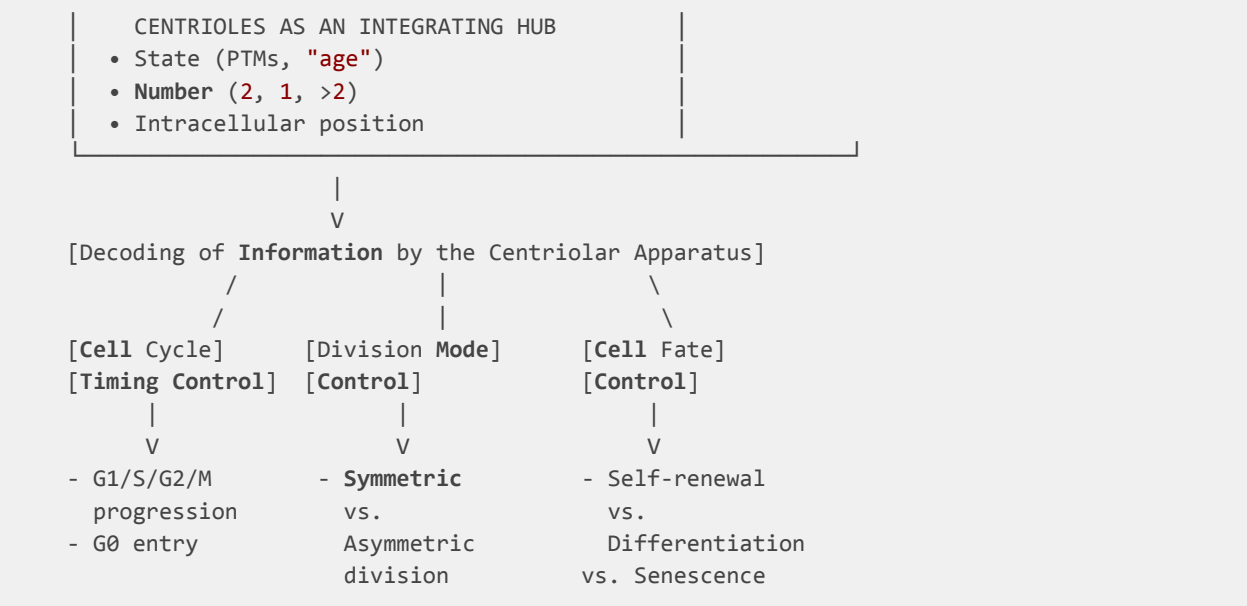
In many adult stem cell compartments (e.g., intestinal crypt, hematopoietic system), the deterministic link between a specific old centriole and a stem cell fate is not as rigorously established as in neural systems. Division patterns may be more probabilistic, regulated by integrated signaling from Wnt, Notch, and Hippo pathways that converge on transcriptional programs. In such an environment, the centriole may act less as an autonomous timer and more as a modulator or integrator—a subcellular compartment that fine-tunes the response to these dominant external signals rather than initiating them de novo (Pitaval et al., 2017). Its role might be to add a layer of historical memory or to ensure the precise spatial execution of a division plan dictated by the niche. This view positions the centriole not as a master switch but as a crucial component of the cellular "hardware" that executes and refines the "software" instructions provided by genetic and signaling networks.

In conclusion, acknowledging these controversies does not invalidate the centriolar timer hypothesis but refines it. It suggests a model where centrioles are privileged, highly conserved timing devices whose causative influence is most prominent in developmental systems requiring precise, iterative counting and robust asymmetric partitioning. In other contexts, they may function as important integrative hubs within a larger, redundant network of cell cycle and fate controls. Future research must focus on designing causal experiments that can isolate timing functions and on mapping the precise molecular dialogue between the centriolar clock and other major regulatory systems to fully define its hierarchical position in cellular decision-making.

An Integrative Model and Conclusions

Synthesizing the evidence from diverse cellular systems, while acknowledging the controversies, allows for the construction of a coherent and predictive framework. We propose a model of "Centriolar Regulatory Clocks," where centrioles function as integrative computational hubs that process temporal and spatial information to guide cellular decisions. This model can be conceptualized as follows:





In this model, external and internal cues converge upon the centriole, whose molecular and physical state—its age-dependent PTM signature, its quantitative number, and its spatial coordinates—serves as a dynamic readout. This integrated information is then decoded by the cell via centriolar-associated complexes (e.g., the PCM, appendages, the cilium) to exert control over three fundamental outputs: the timing of cell cycle phases, the mode of division (symmetric vs. asymmetric), and the ultimate fate choice (proliferation, differentiation, quiescence, senescence). This decoding involves regulating the local concentration and activity of kinases (e.g., PLK1, PLK4, Aurora A), sequestering or releasing transcription factors, and modulating cytoskeletal dynamics and mechanical linkages to the nucleus (Pitaval et al., 2017; Vertii et al., 2016).

Conclusions

The central hypothesis that centrioles act as intracellular timers is substantiated, albeit with important caveats. The weight of evidence confirms that centrioles are not mere passive scaffolds but are critical information-processing hubs. They encode a quantifiable record of cellular history—primarily divisional history through age and number—and integrate this with current signaling status to bias key decisions about the future. They provide a form of structural memory that is physically transmitted to daughter cells.

However, they are not the sole cellular chronometer. Centriolar clocks represent one integral system within a network of interconnected timekeeping mechanisms, including telomere length counters, epigenetic aging clocks, and metabolic oscillators (López-Otín et al., 2023). The unique feature of the centriolar system is its direct physical connection to the division machinery, the cytoskeleton, and major signaling pathways. This allows it to act as both a sensor and an effector, translating temporal information into immediate physical outcomes during mitosis and ciliogenesis. Its dysfunction, therefore, does not simply impair a single process but can corrupt an entire regulatory network governing cellular identity and timing.

Therapeutic Potential

This refined understanding opens novel therapeutic avenues focused on modulating the "centriolar clock." Potential strategies include:

- **Regenerative Medicine**: Pharmacological or genetic "resetting" of centrioles in aged or terminally differentiated cells could, in principle, reactivate a controlled proliferative or regenerative potential. For instance, restoring youthful centriolar integrity in senescent progenitor cells might enhance tissue repair (Shiratsuchi et al., 2022).
- **Oncology**: Cancer cells, particularly cancer stem cells, often exploit and dysregulate centriolar timing. Targeted therapies could aim to forcibly "age" or destabilize their centrioles, triggering irreversible arrest or differentiation. Exacerbating centriole clustering errors in cells with amplified centrosomes presents a promising synthetic lethal approach (Godinho & Pellman, 2014).
- **Anti-Aging Interventions**: Preventing the age-related disintegration of centriolar homeostasis (e.g., loss of cohesion, hyper-amplification) could serve as a strategy to delay cellular senescence and its associated secretory phenotype, thereby promoting tissue healthspan (Mikule et al., 2019).

Final Thesis

In conclusion, centrioles have evolved from simple microtubule-organizing organelles into sophisticated biological "microprocessors." They perform computations based on integrated intra- and extracellular data—essentially "counting" divisions and "gauging" cellular state—and physically implement the cell's "decision" by orchestrating the cytoskeleton, positioning the mitotic spindle, and localizing fate determinants. Their role transcends structure; they are fundamental components of the cellular control system for timing and identity. Consequently, centriolar dysfunction represents more than a broken "part"; it signifies a critical failure in the very system that governs a cell's sense of time and self, with profound implications for development, disease, and aging.

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