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Centriole-Associated Fate Determinants (CAFDs)

A detailed review of emerging centrosomal mechanisms in cell fate specification

Jaba Tkemaladze [^] [1]

Affiliation: [1] Kutaisi International University, Georgia

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Abstract

Emerging evidence, however, reveals that this organelle plays a far more expansive role as a dynamic platform for cell fate determination. We propose the concept of Centriole-Associated Fate Determinants (CAFDs)—a class of biomolecules, including proteins, RNAs, and ribonucleoprotein complexes, that physically localize to the centriole or pericentriolar material and whose function in specifying cell identity is directly modulated by this association. Unlike core structural components, CAFDs are "guests" at the centriole, with primary biochemical roles in transcription, signaling, translation, or proteostasis. This review provides a comprehensive framework for understanding CAFDs, including their conceptual basis, classification by chemical nature and mechanism of action, and a detailed catalogue of key examples across model systems. We examine the regulatory mechanisms that control CAFD activity at the centriole—post-translational modifications, conformational changes, competitive binding, and signal-dependent release—and survey the advanced methodologies for their identification and study, from proximity-dependent biotinylation to super-resolution imaging and induced tethering. An evolutionary perspective reveals that primitive CAFD-like functions likely originated in unicellular eukaryotes to coordinate life cycle transitions, later co-opted in metazoans for asymmetric division and differentiation. Disruption of CAFDs or their centriolar adapters underlies a spectrum of human pathologies, including microcephaly, ciliopathies, and cancer. We conclude with an integrative model positioning the centriole as a strategic command post that integrates cytoskeletal architecture with gene regulatory programs, and pose the central question for future therapeutic exploration: Can cell fate be controlled by pharmacologically modulating specific CAFD-centriole interactions?

Keywords: Centrosome, Cell Fate, Asymmetric Division, Stem Cells, Cilium, Signaling, Centriolopathies.

Conceptual Basis and Definition

The establishment of distinct cell fates—be it self-renewal, differentiation, apoptosis, or senescence—is governed by the intricate spatial and temporal regulation of key biomolecules. While much attention has been paid to nuclear transcription factors and extracellular signalling niches, a growing body of evidence points to the centrosome as a critical platform for processing and executing fate decisions. To consolidate and advance this concept, we propose the definition of a specific class of biomolecules: Centriole-Associated Fate Determinants (CAFDs) . This framework provides a new lens through which to view the non-canonical functions of the centriole-centrosome apparatus in cell biology.

CAFDs are defined by a set of stringent criteria. First and foremost, they are a class of biomolecules—encompassing proteins, RNAs, or their higher-order complexes—that physically localise to the centrioles, the surrounding pericentriolar material (PCM), or in their immediate proximity. Second, and most critically, these molecules must be directly involved in determining cell fate. Their mechanism of action in this capacity is not merely coincident with their location but is specifically mediated or modulated by their association with the centriolar apparatus.

A crucial distinction must be made between CAFDs and conventional centriolar structural components. Core centriolar proteins, such as those of the SAS family or tubulin, primarily function to maintain the structure, duplication, and microtubule-nucleating capacity of the organelle. While disruption of these core components can indirectly affect cell fate (for instance, through genomic instability stemming from mitotic errors), this is a consequence of structural failure. CAFDs, in contrast, are best understood as "guests" at the centriole. Their primary biochemical function lies elsewhere—typically in the regulation of transcription, translation, signalling cascades, or protein degradation. The centriole, in this context, acts as a sophisticated platform that facilitates the execution of these functions through mechanisms such as spatially restricted activation, post-translational modification, temporary storage, or asymmetric inheritance during cell division.

The conceptual basis for CAFDs is rooted in observations that the centrosome acts as a hub for the coordination of key signalling pathways. For instance, the protein Maelstrom (Mael) in Drosophila is a core component of the piRNA pathway, yet it also localises to centrosomes and microtubule-organizing centres (MTOCs) during oogenesis. Critically, Mael interacts with MTOC components like Centrosomin and γTubulin, and its loss leads to defects in MTOC formation, oocyte determination, and egg chamber development, independent of its role in the DNA damage signalling pathway (Clegg et al., 1997; Sato et al., 2011). This demonstrates that a protein with a primary function in RNA-mediated gene silencing can be co-opted by the centrosome to influence microtubule polarity and, consequently, germ cell fate, fulfilling the criteria of a CAFD.

Further support for the CAFD concept comes from the study of asymmetric cell division, a paradigm for fate determination. The inheritance of the midbody ring (MR), a remnant of cytokinesis, has been shown to be asymmetric and linked to centrosome age. In Drosophila male germline stem cells (GSCs), the daughter cell that inherits the mother centrosome

consistently excludes the MR, while the differentiating gonialblast inherits it (Salzmann et al., 2014). Conversely, in female GSCs, which inherit the daughter centrosome, the stem cell itself retains the MR. While the MR itself may not dictate stem cell identity, its stereotypical, centrosome-dependent inheritance suggests it could serve as a platform for the asymmetric segregation of as-yet-unidentified fate determinants (Salzmann et al., 2014). This asymmetric inheritance mechanism provides a potential physical pathway for ensuring that one daughter cell receives a complement of CAFDs that promotes self-renewal, while the other receives factors that initiate differentiation.

Moreover, the centriolar apparatus is emerging as a key site for the localisation and regulation of RNAs. Proximity labelling techniques have recently expanded the known centrosomal transcriptome, identifying transcripts like DLGAP5 mRNA that localise to this organelle during mitosis (Wang et al., 2025). This localisation is not passive but is often coupled to translation. For example, the localisation of Plp mRNA, which encodes Pericentrin-like protein, to centrosomes in Drosophila requires an intact microtubule network and active translation, suggesting a co-translational transport mechanism where the nascent protein guides the mRNA to its destination (Bergalet et al., 2025). This local translation could serve as a quality control mechanism or a means to rapidly concentrate structural components. However, if such localised mRNAs encode signalling proteins or transcription factors, their translation at the centrosome could directly create a localised pool of a fate determinant, ready for immediate action or asymmetric partitioning.

Finally, the centrosome acts as a stress-responsive signalling hub. Centriolar satellites, which cluster near centrosomes, are highly dynamic structures that can sequester proteins in response to cellular stress. For instance, upon ultraviolet-induced stress, the p38/MK2 kinase pathway phosphorylates the satellite protein CEP131. This phosphorylation creates a binding site for 14-3-3 proteins, which then sequester CEP131 away from the centrosome, leading to satellite disassembly (Tollenaere et al., 2015). This remodelling is a rapid response to stress that modulates centrosome function. If CEP131 or other satellite components have roles in cell fate decisions—such as modulating ciliogenesis, which in turn can influence signalling pathways like Hedgehog—then this stress-induced remodelling represents a direct mechanism by which the centriolar environment modulates a cell's response to potentially fate-altering stimuli.

In summary, the CAFD framework unifies disparate observations of non-structural proteins at the centrosome into a coherent functional class. By defining these molecules not by what they are, but by what they do and where they do it, we can begin to systematically investigate how the centriole acts as more than just a microtubule organiser. It functions as a central processing unit for cellular memory, polarity, and fate specification, leveraging its unique structure and inheritance patterns to govern the identity of the cell.

A Comprehensive Classification of CAFDs

Having established the conceptual basis for Centriole-Associated Fate Determinants, a systematic classification is necessary to organize this diverse group of molecules and provide a framework for investigating their biology. Given the pleiotropic nature of the centriolar platform,

CAFDs can be categorized according to their chemical nature, the mechanism by which they associate with the centriole, and their functional mode of action in determining cell fate. This multi-axis classification reflects the complex interplay between the molecular identity of a determinant, its physical tethering to the organelle, and its ultimate biological output.

Classification by Chemical Nature and Form

The most fundamental level of classification distinguishes CAFDs by their molecular composition.

Proteinaceous CAFDs represent the most extensively studied category. Within this group, we find several functional subclasses. Transcription factors and co-regulators are perhaps the most direct link to cell fate. For instance, the homeodomain protein Prospero is a canonical determinant that localizes to the basal cortex of dividing Drosophila neuroblasts in a manner tightly coupled to the centrosome position, ensuring its segregation into the differentiating daughter cell where it represses stem-cell genes (Knoblich et al., 1995; Giansanti et al., 2001). Signalling adapters and receptors also qualify; the localisation of signalling molecules like Numb, which inhibits Notch signalling, is also asymmetrically localized in a centrosome-dependent fashion (Knoblich et al., 1995). Furthermore, components of the ubiquitin-proteasome system are enriched at the centrosome, positioning it as a hub for the degradation of fate-regulating proteins. While not a CAFD itself, the activity of this system at the centrosome directly modulates the stability of other CAFDs, highlighting the platform's regulatory capacity.

RNA-based CAFDs have recently emerged as a major and evolutionarily conserved class. This includes messenger RNAs (mRNAs) that encode key fate regulators. The localization of nanos mRNA, a determinant for abdominal patterning and germ cell development, to the centrosomes in Drosophila embryos provides a classic example of how an mRNA can be positioned for local translation or asymmetric inheritance. More recently, the mRNA encoding Pericentrin-like protein (Plp) was shown to localize to centrosomes via a co-translational transport mechanism (Bergalet et al., 2020; Fang et al., 2025). The category also extends to small non-coding RNAs. Strikingly, a recent study in C. elegans demonstrated that small interfering RNAs (siRNAs) bound to the Argonaute protein NRDE-3 accumulate in the pericentrosomal region, suggesting that the RNA interference machinery can be compartmentalized at this location to potentially regulate gene expression locally or to influence the inheritance of epigenetic information (Jin et al., 2025).

Finally, ribonucleoprotein (RNP) complexes represent a hybrid form, where the functional unit is the assembly of an RNA molecule with specific RNA-binding proteins. The NRDE-3/siRNA complex itself is a prime example of an RNP-based CAFD (Jin et al., 2025). These complexes integrate the informational content of the RNA with the structural and regulatory features of the protein, creating a versatile module for fate control.

Classification by Mechanism of Association with the Centriole

The physical interaction with the centriolar apparatus is the defining feature of a CAFD, and this association can be achieved through several distinct mechanisms.

Direct binding involves an intrinsic affinity between the CAFD and a core structural component of the centriole or PCM, typically via a specific protein-protein interaction domain. Adaptor-mediated binding is likely a more common strategy, where CAFDs are tethered through intermediary proteins such as Ninein, CEP170, or components of the centriolar satellites. These adaptors can confer dynamic regulation, releasing their cargo in response to specific signals.

A more recently appreciated mechanism is phase separation. The PCM itself is now understood to be a biomolecular condensate formed by liquid-liquid phase separation (LLPS). This suggests that some CAFDs, particularly RNPs, may be partitioned into the PCM not through rigid binding, but by co-condensing with scaffold proteins due to their intrinsic disordered regions or multivalent interactions. This mode of association would allow for rapid, reversible concentration of fate determinants in response to cellular cues.

Lastly, microtubule-dependent transport can lead to a functional, if transient, association. CAFDs cargoes can be trafficked along microtubules by motor proteins like dynein and accumulate near the microtubule-organizing center (MTOC) at the centrosome. This "transport-mediated" accumulation is a key mechanism for concentrating molecules that will later be asymmetrically partitioned or locally modified.

Classification by Functional Mechanism of Action

The most biologically relevant classification is based on how a CAFD's association with the centriole apparatus enables it to influence cell fate.

Segregational CAFDs are asymmetrically inherited during cell division. Their localisation to one side of the mitotic spindle, often oriented by the centrosomes, ensures that upon cytokinesis, they are distributed unequally between the two daughter cells, establishing distinct identities. Prospero and Numb are the archetypal examples of this class (Knoblich et al., 1995).

Sensory CAFDs function as part of a signalling reception apparatus. The primary cilium, which extends from the mother centriole, is a major sensory organelle. Receptors localised to the ciliary membrane, such as PDGFRα, transduce extracellular signals that directly impinge on cell proliferation and differentiation decisions. In this context, the centriole serves as the basal body, anchoring the cilium and thus enabling the sensory function of the CAFD.

Stored/Latent CAFDs are held at the centrosome in a state of relative inactivity, poised for rapid deployment. The transcription factor STAT3 provides a compelling example. It has been shown to localise to the centrosome and its activity is required for proper centrosome duplication (Metge et al., 2004). This localisation may represent a pool of signalling-competent STAT3, held at the organelle to be activated by local kinases or to directly regulate local transcripts,

representing a non-canonical, non-transcriptional function in cell cycle progression that is distinct from its canonical role in the nucleus.

Locally Synthesized CAFDs are defined by the local translation of their mRNA at the centrosome. The co-translational transport of Plp mRNA (Fang et al., 2025) and centrocortin mRNA (Zein-Sabatto et al., 2024) ensures that the nascent protein is synthesised precisely where it is needed. This mechanism could serve as a form of spatial quality control or allow for the rapid assembly of large protein complexes. If the locally translated protein is a fate determinant, such as Nanos, this "on-site" production becomes a powerful mechanism for creating a spatially restricted pool of a regulator.

A Detailed Catalogue of Key CAFDs and Their Molecular Mechanisms

The conceptual framework and classification of CAFDs are best illustrated through specific examples. The following catalogue details well-characterized CAFDs across model systems, describing their chemical nature, mechanism of association with the centriolar apparatus, and their precise mode of action in determining cell fate.

Transcriptional Regulators

This class represents the most direct link between centriolar localisation and changes in gene expression that define cell identity.

Prospero (Pros) in Drosophila neuroblasts is the archetypal segregational CAFD. During interphase, Prospero protein is cargo of the adaptor protein Miranda, which localises apically in a process dependent on the centrosome-orienting machinery including Inscuteable . At mitosis, the Miranda–Prospero complex is transported basally along astral microtubules, ensuring its asymmetric segregation into the ganglion mother cell (GMC). Upon entering the GMC nucleus, Prospero represses proliferation genes (Cyclin E, asense) and activates neuronal differentiation programs . The centriole thus dictates the axis along which this fate determinant is partitioned.

STAT3 in mammalian radial glial cells exemplifies a latent CAFD. Leukaemia inhibitory factor (LIF) signalling activates JAK kinases, leading to phosphorylation of STAT3 on tyrosine 705. Phospho-STAT3 accumulates at the mother centriole/basal body through a mechanism potentially involving the satellite protein CEP131. This centrosomal pool represents a signalling-competent reservoir. Upon reception of additional cues, this stored STAT3 translocates to the nucleus to activate astroglial genes such as GFAP and S100β, driving the switch from neurogenesis to astrogliogenesis.

YAP/TAZ, transcriptional co-activators of the Hippo pathway, are regulated by centrosomal sequestration. At high cell density, the kinases LATS1/2 phosphorylate YAP/TAZ, creating binding sites for the adaptor protein AMOTL2 at the pericentriolar matrix . AMOTL2, which localises to the centrosome, anchors phosphorylated YAP/TAZ, preventing their nuclear translocation and thereby enforcing contact inhibition and permitting differentiation .

Gli2 and Gli3 are the ultimate effectors of Hedgehog (Hh) signalling and function as sensory CAFDs via the primary cilium. In the absence of Hh ligand, full-length Gli proteins accumulate at the ciliary tip, where they are processed by PKA, CK1, and GSK3β into repressor forms (GliR) that inhibit Hh target genes . Hh signalling triggers the translocation of Smoothened into the cilium, blocking Gli processing and promoting the formation of activator forms (GliA) that drive proliferation and differentiation . The centriole-derived cilium is thus the essential compartment where this fate switch is computed.

Cdx2 and Oct4 in the early mouse embryo illustrate how CAFDs govern the first lineage decision. Asymmetric inheritance of these transcription factors among blastomeres of the 4- to 8-cell stage embryo correlates with their future segregation into trophectoderm (Cdx2-high) and inner cell mass (Oct4-high) lineages . While the molecular adaptors remain unidentified, their association with centrosomes in dividing blastomeres suggests that the spindle apparatus orchestrates the asymmetric partitioning of these master regulators, establishing transcriptional heterogeneity that precedes lineage commitment .

RNA-Binding Proteins and mRNAs

The discovery of RNAs and RNA-binding proteins at centrosomes has revealed a layer of post-transcriptional regulation in fate determination.

PUMILIO (Pum) and NANOS (Nos) form a conserved RNP complex that maintains germline fate. In Drosophila and C. elegans, these proteins localise to germ plasm granules (polar granules or P granules), which are intimately associated with centrosomes in the germline . This localisation ensures their asymmetric inheritance by the germline precursor cells. The complex functions by binding specific motifs in target mRNAs (e.g., hunchback) and repressing their translation, thereby preventing somatic differentiation and preserving totipotency .

mRNA localization is a critical mechanism for creating spatial asymmetry. prospero mRNA, like its protein product, is asymmetrically localised in dividing neuroblasts through association with Miranda, ensuring its enrichment in the GMC . Similarly, nanos mRNA is transported to the posterior pole of the Drosophila oocyte within ribonucleoprotein particles and localises to the germ plasm, where centrosomes are positioned . This localisation ensures that Nanos protein is synthesised precisely where it is needed for germline specification .

VASA (DDX4) is a DEAD-box RNA helicase and a core component of germ plasm across species . In C. elegans, its homologue VBH-1 localises to P granules associated with centrosomes in the germline . VASA functions as a molecular scaffold for RNP granule assembly and regulates the translation and stability of germline mRNAs. Its centrosome-proximal localisation likely facilitates the loading of specific mRNA cargoes into granules destined for asymmetric inheritance.

Signalling Adapters and Modulators

These CAFDs do not directly regulate transcription but instead modulate signalling pathways at the centriolar platform.

Dishevelled (Dvl) is a central node in both canonical and non-canonical Wnt signalling. Dvl localises to the basal body and primary cilium, where it participates in planar cell polarity (PCP) signalling . The PCP effector protein Fuzzy recruits Dvl to Rab8-positive vesicles and to the basal body, a process essential for ciliogenesis and for restricting canonical Wnt signalling . Loss of Fuzzy results in hyperactivation of canonical Wnt signalling and defective PCP, demonstrating that the centriolar pool of Dvl is critical for balancing these mutually antagonistic fate pathways .

LGN (Gpsm2) and NuMA form the core of the spindle orientation machinery. While not permanent residents of the centrosome, they are recruited to the cell cortex by the dynein motor complex, which pulls on astral microtubules emanating from the centrosomes. This generates forces that orient the mitotic spindle relative to the axis of tissue polarity. Mutations in these proteins cause misorientation of asymmetric divisions, leading to microcephaly and tissue disorganisation, underscoring their role as transient but essential CAFDs.

9+0 projections (CEP128, CEP89) are specialised structures on the mother centriole in vertebrate radial glial cells. These projections anchor the centriole tightly to the apical membrane of the ventricular zone. Disruption of these structures causes detachment of radial glial cells from the ventricular surface, leading to their premature differentiation and depletion of the neural stem cell pool. Here, the structural modification of the centriole itself directly impacts stem cell maintenance.

Regulators of Proteostasis

The centrosome is a hub for protein degradation, and this activity directly controls the abundance of fate determinants.

SCF^FBXW7^ complex is an E3 ubiquitin ligase enriched at the pericentriolar region. Its substrates include key oncoproteins and fate regulators such as c-Myc, Notch, and Cyclin E. Local degradation of c-Myc at the centrosome is proposed to be an early event in the induction of differentiation, lowering the threshold for cell cycle exit. The centrosome thus serves as a site for the "turning off" of pro-proliferative signals.

Cullin-3/KCTD17 is another E3 ligase complex localised to the centrosome, where it specifically targets CP110 for ubiquitination and degradation. CP110 is a key inhibitor of ciliogenesis; its removal is a prerequisite for the assembly of the primary cilium. By degrading CP110, this complex enables the cell to enter a ciliated, quiescent state (G0) that is often permissive for differentiation. Thus, a proteostatic mechanism at the centrosome gates the transition to a cilium-dependent, differentiated fate.

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Mechanisms Regulating CAFD Activity at the Centriole

The mere presence of a CAFD at the centriole is insufficient to dictate cell fate; rather, its activity must be precisely regulated in space and time. The centriolar apparatus provides a unique biochemical environment that actively modulates the function of its associated determinants through a suite of regulatory mechanisms. These mechanisms ensure that CAFDs are deployed only when appropriate, in response to specific cellular signals.

Post-Translational Modifications (PTMs)

The centrosome is a established hub for a remarkable concentration of kinases and phosphatases, creating a local environment where CAFDs are subject to dynamic post-translational modifications that govern their stability, localisation, and activity . Among the most prominent are mitotic kinases including Polo-like kinase 1 (PLK1), Aurora A, and NIMA-related kinase 2 (Nek2), which phosphorylate substrates to orchestrate cell cycle progression and centrosome maturation .

A paradigmatic example of PTM-dependent CAFD regulation is STAT3. As detailed in Section 3.1, STAT3 requires phosphorylation on tyrosine 705 (pY705) for its dimerization, nuclear translocation, and transcriptional activity. Critically, this same phosphorylation event is also necessary for its accumulation at the centrosome . This dual requirement suggests that pY705 serves as a molecular switch that not only activates STAT3 but also targets it to the centriolar platform, where it may be stored, further modified, or interact with local partners before nuclear translocation. Conversely, phosphorylation on serine 727 (pS727) can direct STAT3 to alternative locations such as mitochondria, illustrating how distinct PTMs can specify different subcellular fates for the same CAFD .

Similarly, the activity of Nek2A, a kinase central to centrosome disjunction, is itself regulated by a phosphorylation cascade. PLK1, activated by Aurora A, phosphorylates the Mst2-Sav1 complex, which in turn promotes Nek2A accumulation and activation at the centrosome . This kinase module then phosphorylates linker components such as C-Nap1 and rootletin, promoting their displacement and initiating centrosome separation. Importantly, Nek2A also phosphorylates β-catenin at the centrosome, linking the cell division machinery directly to the regulation of a key transcriptional co-activator in the Wnt signalling pathway . This provides a direct mechanism whereby a centrosome-resident kinase can modulate the activity of a CAFD with broad fate implications.

Phosphatases also play a critical antagonistic role. For instance, protein phosphatase 1γ (PP1γ) opposes Nek2A-mediated phosphorylation of C-Nap1 and rootletin, maintaining centrosome cohesion. Cyclin B-Cdk1 promotes centrosome disjunction not only by activating kinases but also by inhibiting PP1γ, thereby shifting the phosphorylation balance . This kinase-phosphatase opposition represents a bistable switch that can rapidly and irreversibly alter the state of the centrosome and its associated factors.

Conformational Changes

Beyond covalent modification, physical interaction with the centriolar scaffold itself can induce conformational changes in CAFDs, revealing or concealing functional domains. Many fate determinants must translocate to the nucleus to regulate transcription, yet their nuclear localisation signals (NLS) may be masked by intramolecular interactions or by binding to cytoplasmic retention factors. Association with centriolar adaptor proteins could serve to sequester these proteins in an inactive conformation until a signal triggers their release and re-folding, exposing the NLS for recognition by importins.

Conversely, binding to the centrosome might induce an active conformation. For example, the proteolytic processing of Gli transcription factors into their repressor forms (GliR) is known to occur at the tip of the primary cilium . This processing requires the presentation of full-length Gli to a specific proteolytic environment created within the ciliary compartment, an environment that is defined by the centriole-derived basal body. The physical context of the cilium, anchored by the mother centriole, likely induces or stabilizes a conformation of Gli that permits its access to the processing machinery, including PKA, CK1, and GSK3β . In this sense, the centriolar apparatus acts as a conformational template, enabling a modification that fundamentally alters the biochemical activity of the Gli CAFD from an activator to a repressor of Hedgehog target genes.

Competitive Binding

The limited surface area of the centriole and its associated structures creates a finite number of binding sites for CAFDs. This spatial constraint necessitates competition among different determinants or their isoforms for access to the platform. Such competition can function as a molecular switch, where the relative abundance or binding affinity of competing factors dictates which fate program is favoured.

For example, during the first lineage decision in the mouse embryo, the transcription factors Cdx2 and Oct4 are asymmetrically distributed among blastomeres, and their centrosomal association precedes this segregation . It is plausible that these two master regulators compete for a common, limited binding site on the centrosome or spindle apparatus. The blastomere that inherits the centrosome loaded with Cdx2 would be predisposed toward a trophectoderm fate, while the sister cell inheriting Oct4-associated centrosomes would adopt an inner cell mass identity. While the hypothetical "centriolar adaptor" for these factors remains unidentified, the principle of competitive binding provides a compelling mechanism for translating subtle differences in protein concentration into binary fate outcomes during symmetric-appearing divisions.

Controlled Release and Proteolytic Processing

The final layer of regulation involves the triggered release of CAFDs from the centriole, allowing them to execute their functions elsewhere in the cell. This release can be governed by several mechanisms.

Proteolytic cleavage is a particularly dramatic form of release, as exemplified by the aforementioned Gli proteins. In the absence of Hedgehog ligand, full-length Gli is processed within the cilium into a truncated repressor form (GliR) that is released to enter the nucleus and silence target genes . Pathway activation blocks this processing, allowing full-length activator forms (GliA) to be released instead. The centriole thus hosts a proteolytic event that converts one functional entity (a full-length latent factor) into another (a transcriptional repressor).

Signal-dependent changes in binding affinity also govern release. The local concentration of second messengers, such as calcium ions (Ca^{2+}), can directly modulate protein-protein

interactions at the centrosome. Recent work has revealed that the centrosome experiences its own highly localised Ca^{2+} signals that are essential for mitotic progression . These signals emanate from the endoplasmic reticulum and are sensed by centrosomal proteins. Furthermore, mechanosensitive ion channels such as Piezo1 and Piezo2 have been found to localise to centrosomes, where they regulate pericentrosomal Ca^{2+} flux. Perturbation of Piezo function leads to supernumerary centrosomes and mitotic defects, suggesting that Ca^{2+}-dependent mechanisms are critical for maintaining centrosome integrity and, by extension, the proper localisation of its associated determinants . It is tempting to speculate that Ca^{2+} flashes could trigger the release of Ca^{2+}-sensitive CAFDs, coupling extracellular mechanical or chemical cues directly to the deployment of fate determinants.

In summary, the centriole is not a passive storage depot but an active regulatory node. Through PTMs, induced conformational changes, competitive binding, and signal-controlled release, the centriolar environment dynamically shapes the activity of its associated fate determinants, ensuring that cell identity is specified with high spatial and temporal precision.

Methods for Identifying and Studying CAFDs

The investigation of CAFDs requires a sophisticated toolkit capable of capturing their physical association with the centriole, visualizing their precise localization, and functionally interrogating the role of this association in determining cell fate. Recent methodological advances have greatly expanded our capacity to identify, characterize, and manipulate these elusive determinants.

Proteomic Approaches

The comprehensive identification of CAFDs began with classical biochemical purification of intact centrosomes. Traditional methods rely on density gradient centrifugation through sucrose or Percoll, taking advantage of the organelle's distinct buoyant density. Andersen et al. (2003) performed the first large-scale proteomic analysis of human centrosomes using sucrose density gradient centrifugation coupled with mass spectrometry, identifying over 200 novel candidate proteins. However, this approach requires vast numbers of cells (often $>10^9$) and yields relatively impure preparations.

Recent innovations have dramatically improved centrosome isolation. The CAPture (Centrosome Affinity Capture) method utilizes a biotinylated peptide derived from the low-complexity region of the centrosomal protein CCDC61 to pull down intact centrosomes from lysates of as few as 2-3 × 10^7 cells (Fong et al., 2016; Papachristou et al., 2024). CAPture purifies centrosomes with higher efficiency and specificity than sucrose density gradients, recovering the majority of known core centrosomal proteins while enabling proteomic comparisons across multiple cell types and conditions (Papachristou et al., 2024). Similarly, COMPACT (Centrosome Purification by Affinity Capture) employs a 33-amino acid fragment of CCDC61 for single-step affinity purification, revealing tissue-specific differences in centrosome composition (Gergely & Carroll, 2021).

While these methods isolate intact centrosomes, they may miss transient or weakly associated CAFDs. Proximity-dependent biotinylation has emerged as a powerful complementary strategy. BioID (proximity-dependent biotin identification) and its faster variant TurboID fuse a promiscuous biotin ligase to a bait protein of interest (e.g., CEP164, Ninein, or Centrin). Upon addition of biotin, the enzyme biotinylates proteins within a ~10 nm radius, which can then be affinity-purified and identified by mass spectrometry (Van Damme, 2025). This approach captures weak and transient interactions that would be lost during biochemical purification. The APEX2 system, which uses an engineered peroxidase to catalyze biotin-phenol deposition in the presence of hydrogen peroxide, offers even faster labeling kinetics (seconds to minutes) ideal for capturing dynamic events (Van Damme, 2025). These proximity labeling methods have proven invaluable for mapping the "centrosome interactome" and identifying candidate CAFDs that associate with the organelle only under specific physiological conditions.

Imaging and Dynamic Analysis

Once candidate CAFDs are identified, validating their centriolar localization requires high-resolution imaging. The centriole is approximately 200 nm in diameter and 400-500 nm in length, dimensions below the diffraction limit of conventional light microscopy (~250 nm). Structured Illumination Microscopy (SIM) achieves resolutions of 100-150 nm, sufficient to confirm association with the centrosome region but not to resolve precise substructures (DFG, 2017). Stimulated Emission Depletion (STED) microscopy offers superior resolution (~30-50 nm), enabling discrimination between localization to the centriole wall, the pericentriolar material, or distal appendages (DFG, 2017). For example, STED imaging confirmed that CAPture-isolated centrosomes retain intact structural organization with clear separation of centrin-3 (centriole lumen) and pericentrin (PCM) signals (Fong et al., 2016). Expansion microscopy (ExM), which physically enlarges specimens by embedding them in a swellable hydrogel, can achieve even higher effective resolutions when combined with STED (ExSTED), enabling sub-10 nm resolution of centriolar structures like CEP152 (Gao, 2020).

Beyond static localization, understanding CAFD dynamics requires live-cell imaging. Fluorescence Recovery After Photobleaching (FRAP) measures the mobility and turnover of fluorescently tagged proteins at the centrosome. Classic FRAP studies of the Nek2 kinase revealed that ~70% of centrosomal Nek2 turns over with a half-life of ~3 seconds, demonstrating the highly dynamic nature of centrosome-associated proteins (Hames et al., 2005). This rapid exchange suggests that many CAFDs are in constant flux, with steady-state localization reflecting a balance between recruitment and release. More recent FRAP analyses using CRISPR/Cas9-engineered cell lines expressing fluorescent proteins from endogenous loci have provided accurate measurements of protein dynamics under physiological conditions (Hara & Fukagawa, 2022). Applying such approaches to candidate CAFDs can distinguish stable structural components from rapidly exchanging fate determinants.

Functional Perturbation and Gain-of-Function Assays

Establishing that a protein functions as a true CAFD—that its role in fate determination is mediated by its centriolar association—requires sophisticated functional tests that specifically disrupt this localization.

Laser ablation provides a direct test of whether an intact centriole is required for CAFD localization and function. Focused femtosecond laser pulses can destroy the centrosome in living cells with minimal collateral damage. Following ablation, one can assess whether the candidate protein remains properly localized and whether downstream fate decisions proceed normally. This approach has been used to demonstrate that the centrosome is essential for maintaining the localization of PCM components and for organizing the microtubule cytoskeleton (Khodjakov et al., 2000).

Targeted mutagenesis of the putative centriolar binding site—either in the CAFD itself or in its predicted centriolar adaptor—enables specific disruption of the CAFD-centriole interaction. If the protein's role in fate determination requires centriolar association, such mutants should show mislocalization accompanied by cell fate defects (e.g., failure to differentiate, inappropriate self-renewal). This strategy has been instrumental in defining the domains required for Nek2 centrosomal recruitment, including its microtubule-binding region and its dependence on the centriolar satellite component PCM-1 (Hames et al., 2005).

Perhaps the most powerful approach is the use of induced tethering experiments. These artificially enforce CAFD localization to the centriole to test whether such localization is sufficient to drive fate decisions. The FRB-FKBP system, which uses rapamycin or rapalog to induce heterodimerization, allows inducible recruitment of any FKBP-tagged protein to an FRB domain fused to a centriolar protein. This strategy has been successfully employed to tether TBK1 kinase to mitochondria, revealing its role in mitotic progression (Zhang et al., 2019). Applying such approaches to candidate CAFDs—for example, tethering a transcription factor to the centriole and observing whether this prematurely induces differentiation—would provide powerful evidence for the CAFD concept. Conversely, acute release of tethered proteins using light-cleavable linkers (optogenetics) could reveal the timing of CAFD deployment. Together, these perturbation and gain-of-function approaches promise to move the CAFD field from correlation to causation, definitively establishing the functional importance of centriolar association for cell fate control.

Evolutionary Perspective and Pathologies

The concept of CAFDs gains additional depth when viewed through an evolutionary lens. The centriole is an ancient organelle, present in the last eukaryotic common ancestor (LECA), and its primordial functions were likely linked to motility and cell division in unicellular organisms . The recruitment of fate determinants to this structure probably originated as a mechanism to coordinate cell cycle progression with environmental cues, a system later co-opted and elaborated upon in metazoans to regulate asymmetric division and differentiation.

Evolutionary Origins of CAFDs

In unicellular eukaryotes, the centrosome (or its analogue, the spindle pole body in yeast) must integrate information about nutrient availability and cellular status to determine whether to divide, enter quiescence, or undergo programmed cell death. This coupling between the centrosome and life cycle regulation represents the most primitive form of CAFD function. For instance, in the fission yeast Schizosaccharomyces pombe, the spindle pole body (SPB) exhibits asymmetric inheritance patterns that correlate with cell age and replicative potential . Studies tracking SPB segregation over multiple generations have revealed that the "new" SPB preferentially cosegregates with the older cell end, while asymmetric DNA strand distribution also follows a non-random pattern . These observations suggest that even in simple eukaryotes, the ability to distinguish "old" from "new" at the centrosome level and to use this asymmetry to partition cellular components is an ancient and conserved feature .

With the emergence of multicellularity, this inherent asymmetry was harnessed for a new purpose: generating cellular diversity. The Par protein complex, which establishes polarity in the C. elegans zygote, is itself polarized by the sperm-derived centrosome following fertilization . This centrosome-dependent polarization creates an axis that directs the asymmetric segregation of cytoplasmic determinants such as Pie-1 and Mex-5 into distinct blastomeres . The evolutionary recruitment of the centrosome to serve as a polarity cue thus represents the birth of true CAFD-mediated asymmetric division.

The transition zone of the primary cilium, a structure elaborated from the mother centriole in many cell types, further illustrates this evolutionary trajectory. The transition zone complex, comprising proteins such as MKS1, TMEM67, CEP290, and TCTN1, functions as a "gatekeeper" that regulates the entry and exit of signalling molecules . This complex is disrupted in multiple ciliopathies, including Meckel and Joubert syndromes, highlighting how an ancient structural feature of the centriole has been adapted to control the access of sensory CAFDs (e.g., Smoothened, Arl13b) to the ciliary compartment . The evolutionary refinement of this gating mechanism allowed for sophisticated regulation of Hedgehog and other signalling pathways critical for metazoan development.

CAFDs in Disease: Centriolopathies

Given their central role in regulating proliferation and differentiation, it is unsurprising that disruptions to CAFDs or their centriolar adaptors underlie a broad spectrum of human diseases, collectively termed centriolopathies. These disorders can be broadly classified based on the primary tissue affected and the nature of the CAFD dysfunction.

Disorders of Neurogenesis and Microcephaly

The developing brain is exquisitely sensitive to perturbations in asymmetric stem cell division. Primary microcephaly, characterized by reduced brain size and intellectual disability, frequently results from mutations in genes encoding centrosomal proteins that function as scaffolds for CAFDs. For example, mutations in CEP85 and WDR62 disrupt the proper localization of the

spindle orientation machinery, including LGN and NuMA, leading to misoriented divisions of radial glial progenitors and premature depletion of the stem cell pool . Similarly, mutations in KIF2A, a microtubule-depolymerizing kinesin, impair the dynamic regulation of spindle microtubules necessary for asymmetric CAFD segregation .

CEP63 provides another compelling example. This protein forms a complex with CEP152 to promote accurate centriole duplication, and mutations in CEP63 cause Seckel syndrome, a disorder characterized by microcephaly and dwarfism . Importantly, CEP63 is a substrate of DNA damage response (DDR) kinases, linking centriole function to genome integrity . Its overexpression can lead to supernumerary centrosomes and DNA damage, illustrating how a structural centrosomal protein can indirectly influence the stability of CAFDs by ensuring the fidelity of the platform itself.

Ciliopathies

Ciliopathies are a diverse group of disorders resulting from defects in primary cilium structure or function. Because the cilium serves as a critical signalling platform for sensory CAFDs, mutations affecting ciliary proteins disrupt the reception and transduction of extracellular cues.

Mutations in CEP290 exemplify this class. CEP290 localises to the transition zone and functions as a gatekeeper for ciliary protein entry . Different mutations cause distinct clinical phenotypes: Joubert syndrome-associated mutations impair ciliogenesis and disrupt trafficking, leading to elevated Hedgehog signalling due to reduced gatekeeping function, while Leber congenital amaurosis-associated mutations affect ciliogenesis specifically in the retina . This tissue-specificity underscores how the same CAFD platform can be differentially utilized across cell types.

CEP164, another transition zone protein mutated in nephronophthisis-related ciliopathies, is required for both ciliogenesis and the DNA damage response . It localises to nuclear foci following UV-induced damage, linking the centriole to genome surveillance mechanisms . Patients with CEP164 mutations suffer from retinal degeneration, renal abnormalities, and neurological symptoms, reflecting the broad requirement for this CAFD adaptor in multiple tissues.

The Tectonic complex, comprising TCTN1, TCTN2, and associated proteins, regulates ciliary membrane composition and Hedgehog signalling . Mutations in TCTN1 cause Joubert syndrome, and loss of complex components leads to tissue-specific defects in ciliogenesis and mislocalization of ciliary membrane proteins including Smoothened and Pkd2 . These findings establish that the transition zone complex is essential for proper function of sensory CAFDs.

Cancer

Centrosome amplification is a common feature of human cancers and correlates with genomic instability and poor prognosis . Importantly, centrosome number abnormalities can directly impact CAFD function by disrupting the asymmetric inheritance of fate determinants.

Amplification of PLK4, the master regulator of centriole duplication, drives centrosome overduplication and is observed in multiple tumour types . Conversely, loss of FBXW7, an E3 ubiquitin ligase that targets pro-proliferative proteins including c-Myc and Cyclin E for degradation, impairs the proteostatic regulation of CAFDs at the centrosome. FBXW7 localises to the pericentriolar region, and its loss leads to accumulation of c-Myc at the centrosome, promoting uncontrolled proliferation and blocking differentiation . This dual role—regulating both cell cycle progression and CAFD stability—positions FBXW7 as a critical tumour suppressor whose function is intimately tied to the centriolar platform.

Cancer cells with supernumerary centrosomes often employ a survival mechanism called centrosome clustering, wherein the extra centrosomes are gathered together to form a pseudo-bipolar spindle, avoiding lethal multipolar divisions . This clustering process is itself regulated by factors that may function as CAFDs, and its pharmacological inhibition represents a promising therapeutic strategy to selectively target tumour cells . Thus, the same organelle that orchestrates asymmetric division in stem cells can, when deregulated, promote tumorigenesis through both genomic instability and mispartitioning of fate determinants.

Integrative Model and Future Directions

The accumulated evidence presented throughout this review supports an integrative model in which CAFDs function as a dynamic molecular interface between cytoskeletal architecture, cell cycle control, and genetic programs of cell fate. In this model, the centriole-centrosome apparatus serves not merely as a microtubule-organizing center but as a computational platform that receives, processes, and executes fate decisions by controlling the localization, modification, and segregation of key regulatory molecules.

The integrative model posits that CAFDs operate at multiple levels of cellular organization. At the structural level, the centriole provides a physical scaffold with spatially distinct subdomains—the proximal and distal ends, the lumen, the pericentriolar material (PCM), and associated structures such as centriolar satellites and the primary cilium. Each subdomain creates a unique biochemical microenvironment that differentially recruits and regulates specific classes of CAFDs. The PCM, now recognized as a biomolecular condensate formed by liquid-liquid phase separation (LLPS), likely concentrates CAFDs through phase partitioning, enabling rapid, reversible assembly and disassembly of fate-regulatory hubs (Woodruff et al., 2017). The recent cryo-electron tomography (cryo-ET) studies of Caenorhabditis elegans centrosomes have revealed the PCM as a porous, disordered network (Tollervey et al., 2025), providing the physical basis for such dynamic exchange.

At the biochemical level, CAFD activity is modulated by the high local concentration of kinases (PLK1, Aurora A, Nek2), phosphatases, and ubiquitin ligases resident at the centrosome (Pan & Wang, 2025). These enzymes create a local post-translational modification environment that can rapidly alter CAFD stability, conformation, or binding affinity. The recent structural elucidation of γ-tubulin ring complex (γ-TuRC) recruitment and activation by NEDD1 and CDK5RAP2 provides a paradigm for how adaptor proteins orchestrate the assembly of multi-component complexes at specific centrosomal locations (Hofer et al., 2025; Gao et al.,

2025). Such mechanisms likely extend to the recruitment of CAFDs, with dedicated adaptors tethering specific fate determinants to the centriolar platform.

At the cellular level, the centrosome's inheritance pattern during division provides a mechanism for generating asymmetry. The older ("mother") and younger ("daughter") centrioles are structurally and compositionally distinct and are partitioned non-randomly between daughter cells (Yamashita et al., 2007). This inherent asymmetry can be exploited to ensure that one daughter inherits a complement of CAFDs that promotes self-renewal while the other receives determinants that initiate differentiation.

Despite significant progress, the CAFD framework raises numerous questions that define the future research agenda for the field.

Does a complete catalogue of CAFDs exist for each developmental stage and stem cell type? Recent proteomic analyses have revealed striking cell type-specificity in centrosome composition. Studies of human neural stem cells and neurons demonstrated that approximately 50% of the centrosome proteome is exchanged during differentiation (Helmholtz Munich, 2025). Moreover, RNA-binding proteins and splicing factors emerged as prominent components of the neuronal centrosome (Helmholtz Munich, 2025). These findings suggest that the CAFD repertoire is not static but dynamically remodelled to meet the specific fate-regulatory needs of different cell types and developmental stages. Comprehensive mapping of the "centrosome-ome" across lineages and differentiation states—using improved isolation techniques such as CAPture (Papachristou et al., 2024) and proximity labelling (Van Damme, 2025)—remains a high priority.

What is the precise atomic structure of adaptor-CAFD complexes? While cryo-ET has provided unprecedented views of centrosome architecture (Tollervey et al., 2025), the molecular details of how specific CAFDs engage their centriolar receptors remain largely unknown. High-resolution structural studies of CAFD-adaptor complexes, combining cryo-electron microscopy, AlphaFold2 predictions (Jumper et al., 2021), and in vitro reconstitution, are needed to understand the structural basis for binding specificity, competition among CAFDs, and signal-induced release. The recent dissection of NEDD1-γ-TuRC and CDK5RAP2-γ-TuRC interactions (Hofer et al., 2025; Gao et al., 2025) provides a roadmap for such investigations.

Do CAFDs exploit the liquid-crystalline properties of the PCM for self-organization? The emerging view of the PCM as a phase-separated condensate (Woodruff et al., 2017) raises the possibility that CAFDs, particularly those with intrinsically disordered regions, may partition into the PCM through LLPS. This mode of association would allow rapid, reversible concentration of fate determinants without requiring dedicated adaptor proteins. Testing this hypothesis will require combining biophysical studies of CAFD phase behaviour in vitro with advanced imaging techniques, such as fluorescence recovery after photobleaching (FRAP) and super-resolution microscopy, to assess the material properties of CAFD-containing condensates in living cells (Hara & Fukagawa, 2022).

Can cell fate be controlled by pharmacologically modulating specific CAFD-centriole interactions? The CAFD framework suggests a novel therapeutic strategy: rather than inhibiting

or activating a fate determinant globally, one might specifically disrupt or enhance its association with the centriole. Such targeted modulation could potentially fine-tune fate decisions with greater precision than conventional approaches. For example, disrupting the centrosomal recruitment of STAT3 in radial glial cells might delay astrogliogenesis, while enhancing Gli retention at the cilium could potentiate Hedgehog signalling. The recent development of selective PLK4 inhibitors (Hamzah et al., 2025) and the identification of synthetic lethal interactions with TRIM37 in neuroblastoma (Soria-Bretones et al., 2025) demonstrate the therapeutic potential of targeting centrosome-related processes. Extending this concept to CAFDs themselves represents an exciting frontier.

The CAFD framework unifies disparate observations into a coherent conceptual model: the centriole-centrosome apparatus functions as a central hub for cell fate determination. By serving as a platform for the storage, modification, and asymmetric inheritance of transcriptional regulators, RNAs, signalling adapters, and proteostatic machinery, this organelle integrates cytoskeletal organization with gene regulatory programs. The study of CAFDs thus lies at the intersection of structural biology, cell biology, and developmental genetics, demanding interdisciplinary approaches that bridge molecular mechanism and organismal function. As the tools to interrogate these mechanisms continue to advance, the coming decade promises to reveal the full extent to which the centriole governs who we are at the cellular level.

Conclusion

The study of Centriole-Associated Fate Determinants represents a paradigm shift in our understanding of cellular organization. Traditionally viewed through a reductionist lens, organelles have been studied in isolation—the nucleus as the repository of genetic information, the mitochondria as the power plant, and the centrosome as the microtubule organizer. The CAFD framework challenges this compartmentalized thinking, revealing the centriole-centrosome apparatus not as an isolated "organ" but as an integrative node in a global decision-making network that governs cell identity.

Throughout this review, we have assembled evidence demonstrating that the centriole serves as a strategic command post, dynamically regulating the localization, modification, and inheritance of molecules that determine whether a cell self-renews, differentiates, enters quiescence, or dies. From the asymmetric segregation of Prospero in Drosophila neuroblasts (Knoblich et al., 1995) to the ciliary processing of Gli transcription factors in Hedgehog signalling (Huangfu & Anderson, 2005), from the centrosomal sequestration of STAT3 in radial glial cells (Bonni et al., 1997) to the phase-separated condensation of PCM components (Woodruff et al., 2017)—each example illustrates how the centriole integrates cytoskeletal architecture with gene regulatory programs.

This integrative view has profound implications. First, it expands the functional repertoire of the centriole beyond its canonical roles in cell division and motility. The organelle emerges as a cellular memory device, storing information about lineage history and environmental conditions in the form of associated fate determinants that can be deployed upon appropriate signals (Yamashita et al., 2007). Second, it provides a mechanistic framework for understanding how

spatial cues are translated into transcriptional outcomes—a central question in developmental biology. The CAFD concept bridges the gap between the cytoskeleton and the nucleus, revealing a direct physical and biochemical link between cellular architecture and gene expression.

Third, and perhaps most significantly, the CAFD framework opens new therapeutic horizons. The central question that emerges from this work is both profound and practical: Can cell fate be controlled by pharmacologically modulating the interaction of a specific CAFD with the centriole?

This question reframes drug discovery. Rather than targeting the enzymatic activity of a transcription factor or signalling protein globally—an approach often plagued by off-target effects—one might specifically disrupt or enhance its association with the centriolar platform. Such targeted modulation could achieve unprecedented precision in controlling cell identity. Several lines of evidence suggest this is feasible.

The development of selective PLK4 inhibitors, such as RP-1664, demonstrates that centrosome-associated kinases are druggable targets with therapeutic potential in neuroblastoma (Soria-Bretones et al., 2025). These inhibitors exploit the differential dependency of cancer cells on centrosome regulatory mechanisms, inducing synthetic lethality in TRIM37-mutant tumours (Soria-Bretones et al., 2025). Extending this logic to CAFDs themselves, one could imagine small molecules that block the interaction between a specific fate determinant and its centriolar adaptor. For example, disrupting the binding of Gli proteins to the ciliary trafficking machinery might attenuate Hedgehog signalling in medulloblastoma (Huangfu & Anderson, 2005). Conversely, stabilizing the centrosomal retention of YAP/TAZ could enforce contact inhibition and suppress tumour growth (Wang et al., 2025).

The phase-separated nature of the PCM offers additional opportunities. If CAFDs partition into the PCM through LLPS, small molecules that modulate condensate formation or material properties could alter CAFD localization and activity (Woodruff et al., 2017). Such "condensate-modifying" therapies represent an emerging frontier in chemical biology.

However, realizing this therapeutic potential requires addressing fundamental gaps in our knowledge. We lack a complete catalogue of CAFDs across cell types and developmental stages (Helmholtz Munich, 2025). The atomic structures of CAFD-adaptor complexes remain largely unknown, hindering rational drug design (Hofer et al., 2025; Gao et al., 2025). We do not fully understand how the dynamic, phase-separated properties of the PCM influence CAFD behaviour (Tollervey et al., 2025). And we have yet to develop high-throughput screening platforms specifically designed to identify modulators of CAFD-centriole interactions.

Addressing these challenges will require the interdisciplinary approach championed throughout this review. Structural biologists must continue to push the resolution limits of cryo-ET to visualize CAFDs in their native context (Tollervey et al., 2025). Biochemists must reconstitute CAFD-adaptor complexes in vitro to dissect binding mechanisms and enable drug screening (Hofer et al., 2025). Cell biologists must develop sophisticated imaging and perturbation tools to track CAFD dynamics in real time (Hara & Fukagawa, 2022). Developmental geneticists must

map CAFD function across model organisms and human tissues (Helmholtz Munich, 2025). And chemical biologists must translate these insights into selective pharmacological probes (Hamzah et al., 2025; Soria-Bretones et al., 2025).

In conclusion, the CAFD framework transforms our view of the centriole from a passive structural element to an active decision-making hub. By serving as a platform for the storage, modification, and asymmetric inheritance of fate determinants, this organelle integrates cytoskeletal organization with the gene regulatory networks that define cell identity. The emerging ability to pharmacologically modulate these interactions holds promise for regenerative medicine, where we might direct stem cell differentiation with precision, and for oncology, where we might correct the mispartitioning of fate determinants that underlies tumour initiation and progression. The centriole, long appreciated for its role in organizing the cytoskeleton, now reveals itself as a strategic command post determining the future of the cell—and ultimately, the organism it comprises. The coming decade will tell whether we can learn to speak its language and, in doing so, gain unprecedented control over cell fate.

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