Trends in Neurosciences

CellPress OPEN ACCESS

Review

Non-canonical roles of mitotic proteins in cortical neurons

Joana Cavaco[1,2] and Sara Carvalhal[1,2,*]

Mitotic proteins are traditionally studied for their role in chromosome segregation during cell division. However, research increasingly highlights the important non-canonical roles of mitotic proteins beyond mitosis, particularly in the mammalian cerebral cortex. Alterations in the expression levels or mutations of mitotic proteins are increasingly linked to brain disorders such as primary microcephaly and Alzheimer's disease. A central, unresolved question remains: how do mitotic proteins contribute to neuronal pathogenesis? Here, we review emerging literature on the non-canonical roles of mitotic proteins in mature neurons. Additionally, we discuss how these contribute to the complex mechanisms underlying neurodevelopmental and neurodegenerative disorders. We also discuss their potential for identifying therapeutic strategies and as biomarkers in brain pathologies.

Highlights

Although neurons are post-mitotic, many mitotic proteins remain expressed in the adult mammalian brain, particularly in the cerebral cortex.

Beyond their role in cell division, mitotic proteins have non-canonical functions in cortical neurons, impacting neuronal migration, architecture, and functional modulation.

Altered expression or mutations of mitotic proteins are increasingly linked to brain disorders, including primary microcephaly and Alzheimer's disease.

Current models of neurodevelopmental disorders often overlook how the non-canonical functions of mitotic proteins may disrupt neuronal generation and maintenance, and potentially the organisation of neural circuits. The role of mitotic proteins in neurodegenerative disorders remains controversial, particularly regarding their direct impact on disease pathways.

Mitotic proteins in the brain

One of the most exciting recent findings in **mitosis** (see Glossary) research is that mitotic proteins are widely expressed across various types of cell, including brain cells. This widespread expression is particularly intriguing, given that the adult brain consists predominantly of post-mitotic cells. Recent advancements in single-cell and spatial transcriptomics have enhanced our understanding of the brain's molecular complexity, facilitating the identification of novel contributors to neural function and pathology, including mitotic proteins [1–3]. Genomic, transcriptomic, and proteomic studies have identified recurrent mutations or regulatory alterations (e.g., under- or overexpression) of mitotic proteins in neurological disorders, such as autosomal recessive primary microcephaly (MCPH) and neurodegenerative diseases, such as Parkinson's disease (PD) [4–14]. Together, these findings indicate that mitotic proteins play a role in neuronal physiology and pathogenesis. Mitotic proteins are primarily known for facilitating proper chromosome segregation (Figure 1; [15]), where several mitosis-driven models have been proposed to explain their contribution to neurodevelopmental and neurodegenerative disorders [16,17]. However, accumulating evidence shows that they also perform diverse functions in post-mitotic neurons, referred to as non-canonical roles (Figure 1). Most of our knowledge regarding non-canonical functions of mitotic proteins stems from studies in which they have been examined in isolation, or in the limited context of specific pathways or cellular processes [9,18]. This highlights the need to investigate these non-canonical functions in more complex physiological settings. This review examines current research on non-canonical roles of mitotic proteins in fully differentiated cortical neurons and their involvement in neuronal pathogenesis. We focus primarily on mammalian research, particularly on the neocortex, with occasional examples from studies in non-mammalian models. Finally, we discuss how studying mitotic proteins beyond mitosis could contribute to advancing therapeutic strategies and identifying biomarkers in diseased neurons.

The 'classical' role of mitotic proteins in neurogenesis

Direct and indirect neurogenesis contribute to a hierarchy of differently fated cell types, leading to neocortex complexity [19]. Indirect neurogenesis generates brain cells for all cortical layers, with

[1]Algarve Biomedical Centre – Research Institute (ABC-Ri), Universidade do Algarve, Campus de Gambelas, Faro 8005-139, Portugal
[2]Algarve Biomedical Centre (ABC), Universidade do Algarve, Campus de Gambelas, Faro 8005-139, Portugal

*Correspondence:
sibandarra@ualg.pt (S. Carvalhal).

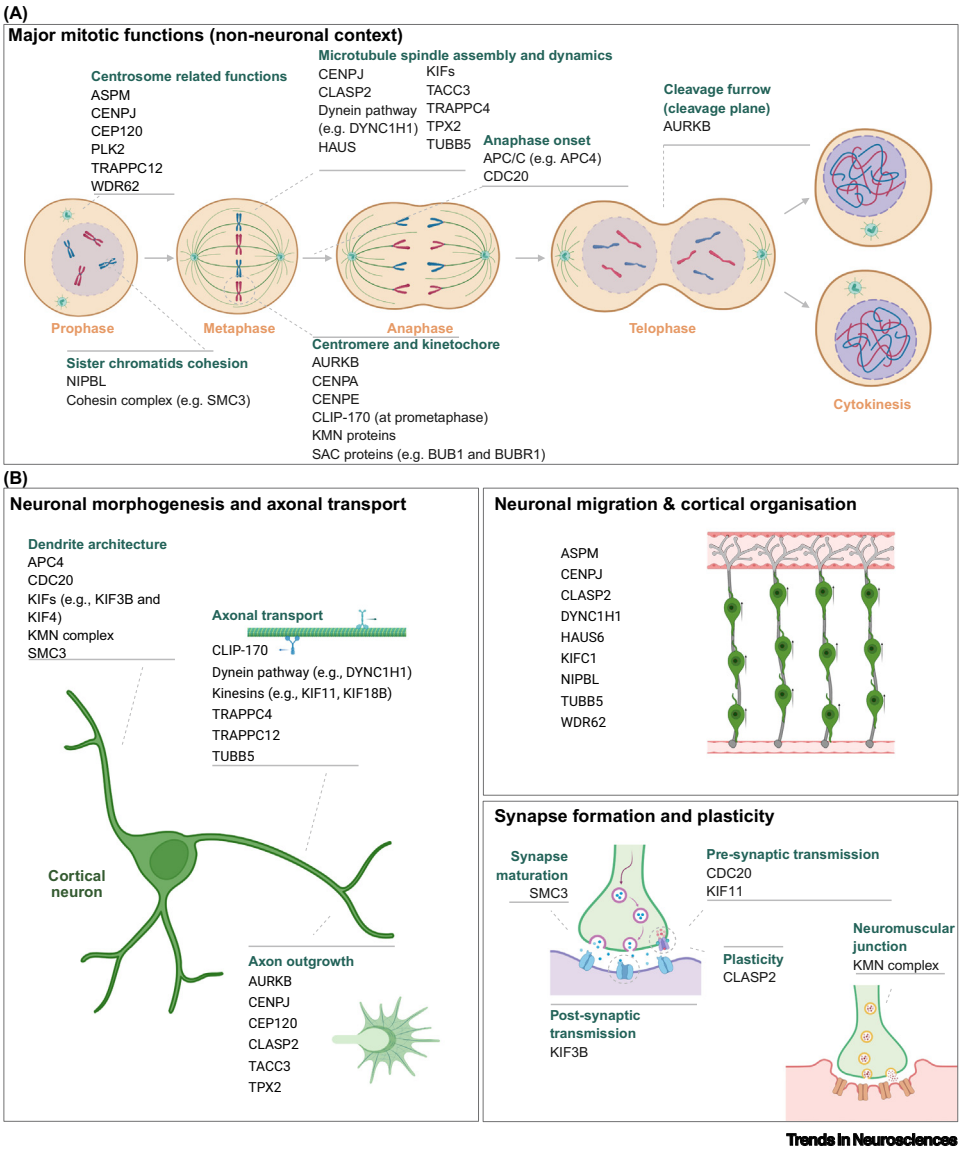

Figure 1. Canonical and non-canonical roles of mitotic proteins. (A) Schematic overview of major canonical mitotic functions. Mitotic proteins coordinate key processes during each mitotic phase (dark yellow), including centrosome-related functions (depicted in light green), spindle assembly and dynamics (depicted in dark green), and chromosome segregation (depicted in red and blue). For simplicity, not all mitotic proteins are annotated with their mitotic functions. In most cases, these roles have been exclusively inferred from studies conducted in non-neuronal cells [5,16,17,70,72,100,129,132,133]. (B) Overview of non-canonical functions of mitotic proteins in differentiated cortical neurons. Experimental evidence supports the involvement of mitotic proteins in neuronal morphogenesis and axonal transport (top left), neuronal migration and cortical organisation (top right), and synapse formation and plasticity (bottom right). Abbreviations: APC, anaphase-promoting complex; ASPM, abnormal spindle-like microcephaly protein; BUB1, budding uninhibited by benzimidazoles 1; BUBR1, budding uninhibited by benzimidazoles-related 1; CDC20, cell division cycle protein 20; CENP, centromere protein; CEP, centrosomal protein; CLASP2, cytoplasmic linker-associated protein 2; CLIP, cytoplasmic linker protein; HAUS, Augmin-like complex subunit; KIF, kinesin-like protein; KMN, KNL1/MIS12 complex/NDC80 complex network; NIPBL, Nipped-B-like protein; PLK2, polo-like kinase 2; SAC, spindle assembly checkpoint; SMC3, structural maintenance of chromosomes protein 3; TACC3, transforming acidic coiled-coil-containing protein 3; TPX2, TPX2 microtubule nucleation factor; TRAPP, trafficking protein particle; WDR62, WD repeat-containing protein 62. Figure created in BioRender (biorender.com). Carvalhal, S. (2025) https://BioRender.com/hw7c409.

Glossary

Anaphase-promoting complex/cyclosome (APC/C): a multiprotein E3 ubiquitin ligase that promotes sister chromatid separation and mitotic exit by targeting regulatory proteins for degradation.

Aneuploidy: a condition characterised by an abnormal chromosome number, either gains/losses of whole chromosomes, or non-balanced rearrangements of chromosomes, such as deletions, amplifications, or translocations of large regions of the genome.

Canonical functions: in the context of protein function, canonical function refers to the originally described and well-characterised role of a protein. In the current article, the term refers to mitotic roles discovered in dividing cells, whereas non-canonical functions refer to the mitotic protein roles performed outside the mitotic process.

Centrosome: centrosome functions as a microtubule-organising centre, facilitating the assembly of bipolar spindle microtubules and defining spindle polarity.

Chromosomal instability: increased rate of chromosomal alterations, which can be numerical or structural.

Cleavage plane orientation: the direction of the cleavage furrow that forms to separate the newly formed daughter cells. Typically, the cleavage furrow forms after anaphase.

Cohesin complex: a ring-shaped protein complex that mediates sister chromatid cohesion by physically entrapping DNA fibres until separation is triggered. The human mitotic cohesin complex is composed of two structural maintenance of chromosomes (SMC) proteins, SMC1A and SMC3, an α-kleisin subunit, RAD21, and a subunit from the STAG protein family.

Kinetochore: a large proteinaceous structure that mediates the interactions between chromosomal DNA and the spindle microtubules. The KMN (named for the Knl1 complex, the Mis12 complex, and the Ndc80 complex) network is part of the protein architecture within kinetochores. Kinetochore functions include attachment of chromosomes to the microtubules (see kinetochore–microtubule attachments) and monitoring the quality of those

the neurogenic pool predominantly contributing to the production of upper-layer projection neurons [19,20]. Although conventionally believed to be deterministically decided, recent studies suggest that cell fate during neurogenesis involves stochastic processes [21]. Hence, the outcome is governed in part by randomness yet remains remarkably precise and robust. Additionally, apoptosis regulates the neurogenic pool by programmed cell death. The removal of these cells maintains normal tissue-size homeostasis across distinct neuronal cell types [17,22]. Longer proliferative activity is associated with increased brain complexity, as shown in mice and other rodents, a principle presumed to be the same in other species, including humans [19]. Errors in chromosome segregation during neurogenesis are a source of **chromosomal instability** and **aneuploidy** [23]. On one hand, this triggers apoptosis due to incompatibility with cell fitness or neuronal function disruption, leading to reduced cell complexity. On the other hand, longer proliferative activity raises the probability of mitotic errors, potentially increasing the background noise of the stochastic nature of neurogenesis. Although mechanisms to correct mitotic errors are well studied in somatic cells – for example, **spindle assembly checkpoint** (**SAC**) – their efficiency in human neural stem cells (NSCs) and neural progenitor cells (NPCs) remains poorly determined [24]. Aneuploidy and chromosomal instability are not limited to the developmental stage – they are also present during adult neurogenesis and/or in mature neurons [23,25,26]. Aneuploid and euploid neurons coexist in developing and adult mammalian nervous systems [25–27]. These findings challenge the traditional view that aneuploidy is incompatible with neuronal survival and function. Yet, the functional implications of an adult brain composed of intermixed aneuploid and euploid cells and associated apoptosis remain to be clarified [25–27]. Similarly, the roles of non-canonical mitotic protein functions at this stage remain largely unknown.

Non-canonical functions of mitotic proteins in cortical differentiated neurons

Neuronal migration and cortical organisation

Neuronal migration is one of the most fundamental processes in constructing functional brain circuits during development [28]. Perturbations in this process can lead to circuit dysfunction or malformation, contributing significantly to the aetiology of various neurodevelopmental disorders [29,30]. Under certain postnatal abnormal conditions, such as brain injury, neuroblast migration is reactivated [31], allowing these immature cells to migrate to damaged areas and commit to becoming neurons [32].

Centromere protein J (CENPJ) is a protein expressed in postmitotic neurons within the cortical plate and acts during their radial migration [33]. These alterations are attributed to CENPJ's critical role in assisting microtubule destabilisation, a process essential for effective neuronal migration [33]. The migration of mouse cortical neurons also depends on Nipped-B-like protein (NIPBL) [34], a regulator of cohesin loading and distribution on the genome before mitosis [35]. In cortical neural progenitors, depletion of NIPBL disrupts the expression of key migration-related genes, including *Sema3a*, *Nrp1*, *Plxnd1*, and *Gabbr2* [34].

In vivo studies in mice have shown that depletion of Augmin-like complex subunit 6 (HAUS6), a mediator of branching microtubule nucleation, disrupts neuronal migration. Depletion caused retention of neurons in the subventricular and intermediate zones [36,37]. Similarly, mouse *in vivo* studies have shown that reduced levels of the abnormal spindle-like microcephaly protein (ASPM) impair neuronal migration, causing stalled neurons in the intermediate zone that fail to reach the cortical plate [38]. Mutations in the *ASPM* gene are the most common cause of MCPH, characterised by microcephaly at birth and nonprogressive intellectual disability [38].

Variants on the Cytoplasmic linker-associated protein 2 (*CLASP2*) gene are connected with intellectual disability [39]. CLASP2 has been identified as a cytoskeletal effector in the reelin

attachments through activating a signalling (SAC) pathway.
Kinetochore–microtubule attachments: the connections of each kinetochore of each sister chromatid to microtubules. The kinetochore can sense the wrong attachment of chromosomes to spindle microtubules.
Mitosis: a dynamic and coordinated process that ensures equal inheritance of duplicated chromosomes into two daughter cells. It is conventionally divided into prophase, metaphase, anaphase, telophase, and cytokinesis.
Mitotic spindle: a bipolar microtubule-based scaffold that self-assembles and ensures accurate capture, alignment, and segregation of chromosomes during mitosis. The microtubule dynamics are controlled by motor and non-motor microtubule-associated proteins (MAPs). While motor MAPs, like kinesin and dynein, drive cellular cargoes toward microtubule ends, non-motor MAPs primarily act as structural elements on the microtubule dynamics, turnover, and stability.
Spindle assembly checkpoint (SAC): a highly regulated signalling network functioning as a surveillance mechanism that delays mitotic progression until all chromosomes are properly attached to the spindle, for instance, in the presence of unattached or misaligned kinetochores.

signalling pathway important for the regulation of neuronal migration, but also dendritic growth and branching, dendritic spine formation, synaptogenesis and synaptic plasticity [40,41]. In mice, *Clasp2* knockdown induced neuronal mislocalisation within cortical layers [42], possibly due to CLASP2 facilitating dynamic actin filament organisation along the microtubule lattice [43].

Major morphological and physiological transitions underlie the formation of functional cortical circuits, including both permanent architectures and transient developmental configurations [44]. Studies in mice and rats show that kinesin-like protein (KIFC1) is crucial for guiding neurons to follow the correct migration route: when KIFC1 is depleted in neurons, they deviate from the correct direction, due to altered growth cone morphology and axonal growth [45,46]. Tubulin beta 5 (TUBB5), which is highly expressed in mouse NPCs and neurons during embryonic development, regulates leading process extension; its knockdown shortens this structure and disrupts it, altering the migration from the ventricular zone to the cortical plate [47,48]. Defective neuronal migration patterns were also described in patients carrying mutations in the Dynein cytoplasmic 1 heavy chain 1 (*DYNC1H1*) gene [49]. DYNC1H1 protein serves as a core complex for retrograde trafficking in neuronal axons. Variants in the *DYNC1H1* gene have been implicated in microcephaly and motor neuropathies, where some patients exhibit progressive neurodegenerative features [50]. Patients with WD Repeat Domain 62 (WDR62) mutation (MCPH2) carry a wide spectrum of cortical malformations, including immature radial columnar organisation, and heterotopia in the intermediate zone, suggestive of problems in neural migration [51]. The diverse roles of WDR62 in dividing and non-dividing cells suggest its importance in various aspects of brain development and maintenance [52].

Dendrite morphogenesis

The organisation of the neuronal architecture – from dendrite growth and branching to the axonal domain – integrates the synaptic connectivity within networks. This creates a neuronal heterogeneity architecture which allows for diverse and complex neuronal interactions, ultimately shaping brain circuits and function [28]. Heterozygous knockout of Structural Maintenance of Chromosomes 3 (SMC3), a subunit of the **cohesin complex**, has been shown to reduce dendritic density in the cerebral cortex of mice [35,53]. Anaphase-promoting complex 4 (APC4) and Cell division cycle protein 20 (CDC20) are both pivotal to the transition of metaphase to anaphase: *Apc4* knockdown increased the number of neurites exiting the somata of mouse cortical neurons, and Cdc20 knockdown significantly reduced dendrite length in rat granule neurons of the cerebellar cortex [9,54].

Kinesins (KIFs) comprise a large superfamily of molecular motors expressed in both mitotic and post-mitotic cells [18]. KIFs regulate microtubule dynamics and facilitate the intracellular transport of organelles, mRNAs, and protein complexes along microtubules. In the nervous system, they are expressed in both mitotic and post-mitotic cells, where they perform essential functions [18]. For example, KIF3B knockdown in primary mouse cortical neurons increased dendritic branching and spine density [55]. Also, KIF4 regulates neuronal cell death through activity-dependent survival in the murine central nervous system [56]. It facilitates the transport of specific proteins to the distal part of the neurite in a microtubule-dependent manner [57]. KIF4-mutant mice exhibited aberrant morphology in dendrites and mild developmental delay [56]. Beyond the previously mentioned role of KIFC1 in regulating growth cone morphology and axonal growth, other studies have also described the functions of various KIFs in neuronal cells, including KIF2C, KIF6, KIF11, KIF12, and KIF23 [18,45,46,58]. These studies challenge the traditional view that 'mitotic' proteins function exclusively in dividing cells, extending the concept of mitotic machinery being repurposed in post-mitotic neuronal cells. Another compelling example is the KNL1/MIS12 complex/NDC80 complex (KMN) network, a highly conserved and extensively studied network due to its critical role in safeguarding proper chromosome segregation. Studies uncovered roles for KMN proteins in

nervous system development independent of their mitotic functions in *Drosophila* and *Caenorhabditis elegans*, respectively, in dendrite outgrowth and branching [59,60].

Axon outgrowth

Centrosome-dependent microtubule modifications set the conditions for axon outgrowth, a critical process in the establishment and maintenance of the spatial architecture of neuronal circuits [28,61]. Centrosomal protein of 120 kDa (CEP120) downregulation in mouse embryos via shRNA impaired microtubule organisation, increased centrosome motility, and disrupted the dynamic behaviour of axon formation [62]. The functions of CLASP2 and CENPJ, two proteins mentioned earlier, are not limited to neuronal migration: CLASP2 knockdown in cortical and hippocampal neurons increased axon length, accelerated outgrowth, and premature axon formation [41,43]; *Cenpj* shRNA in mouse cultured neurons enhanced axon growth and branching [33]. Both *in vivo* and *in vitro* mouse models suggest a potential role for CENPJ in promoting axonal growth – but not in the early steps of axonogenesis [33]. CLASP2 and CENPJ findings suggest that multiple mitotic proteins may act as modulators of axonal growth.

Findings from non-mammalian species lend further support for this notion. For instance, impairment of Aurora kinase B (AURKB) in zebrafish (*Danio rerio)* led to altered axon morphology, including truncated axons and abnormal branching [63]. In opposition, overexpression of AURKB accelerated axonal growth [63]. AURKB is found in post-mitotic neurons of zebrafish and shows increased accumulation in primary neurons of anaphase-promoting complex (APC) mutant mice, supporting a post-mitotic role for this kinase across species [63,64].

Inhibition of the transforming acidic coiled-coil-containing protein 3 (TACC3) in *Xenopus laevis* cultured neurons reduced the number of formed axons and their length [65]. Moreover, *X. laevis* embryos depleted of TACC3 or overexpressing TACC3 both displayed spinal cord axon stability and guidance defects [66]. TACC3-depleted axons in *X. laevis* embryonic neurons significantly decreased axon outgrowth velocity and increased axon retraction rate [67]. This indicates that TACC3's role in axon formation may depend more on maintaining optimal expression levels and on developmental-stage context. In cultured rat neurons, TPX2 microtubule nucleation factor (TPX2) expression was shown to peak during early dendrite development and TPX2 depletion increased the rate of neurite outgrowth on these neurons [68] (although the distinction between axons and dendrites was unclear in this set of experiments). In mice, the hyaluronan-mediated motility receptor (HMMR) mediates the localisation of TPX2 to neurons [69]. Supporting a role of TPX2 in the neurites, overexpressing HMMR in these neurons increased axon and dendrite outgrowth, whereas its depletion resulted in the opposite phenotype [69]. These studies highlight TPX2 as a potential regulator of neuronal morphology and circuit formation, although the specific mechanisms remain to be fully elucidated.

Axonal transport

Axonal transport is essential for neural function effective network connectivity. This highly coordinated process relies on motor proteins that allow bidirectional movement of RNAs, vesicles, and organelles along microtubules [70,71]. The roles of kinesins and dynein in these processes are well established: kinesin motors transport cargos toward the distal tip (the anterograde direction), whereas dynein motors drive them back to the cell body (the retrograde direction) [18,70,72–74]. KIF11, also known as kinesin spindle protein (KSP) or Eg5, greatly exemplifies a protein with overlapping functions in axonal transport and mitosis [75–77]. KIF11 holds essential activities in mitotic cell division, particularly in bipolar spindle formation and centrosome separation [75]. Beyond its mitotic functions, recent studies in *Drosophila* suggest that KIF11 acts as a brake on kinesin-1-driven microtubule sliding [78]. Similarly, DYNC1H1, a component of the dynein pathway, exemplifies how

proteins traditionally associated with axonal transport are also involved in mitosis. Mutations in *DYNC1H1* identified in patients are associated with a broad spectrum of overlapping features characteristic of both neurodevelopmental and neurodegenerative disorders [50,79,80]. A *Dync1h1* knock-in mouse carrying a pathogenic DYNC1H1 mutation exhibited severe cortical defects and showed increased cell death of radial glia cells [80]. Complementary studies in human-derived induced cortical neurons showed that DYNC1H1 and its cofactor dynactin are capable of moving along the entire length of the axon but are delivered separately to the axon tip [81]. Another example is the cytoplasmic linker protein-170 (CLIP-170) that operates in the initiation of dynein retrograde axonal transport and contributes to **kinetochore–microtubule attachments** during mitosis [70,72,82]. In addition, *Tubb5* knockdown in murine cortical neurons reduced the number of dendritic spines and disrupted microtubule trafficking [48]. This supports TUBB5's function in regulating proper dendritic density and morphology, possibly through microtubule dynamics. Considering that *Tubb5* suppression also affects **mitotic spindle** orientation, further studies are needed to disentangle how these processes contribute to the microcephaly and structural brain abnormalities associated with *TUBB5* mutations [5,47,48,83].

Synapse formation and plasticity

Several proteins discussed in the preceding text are critical for synapse formation and function. In the cerebral cortex of *Smc3* heterozygous mice, in addition to changes in dendritic density, an increased number of immature synapses was observed [53]. Similarly, CLASP2 overexpression increased the synaptic area and the number of synapses of primary mouse neurons [84]. These findings propose that CLASP2 participate in synaptogenesis and synaptic plasticity. KIF3B has been shown to modulate excitatory post-synaptic transmission by regulating the distribution of Postsynaptic density protein 95 (PSD95) [55]. KIF11 knockdown enhanced presynaptic mediators of synaptic transmission in primary mouse hippocampal neurons [77]. Both findings support the participation of KIFs in synaptic plasticity [18,77]. Perturbations in the *Drosophila* orthologs of KMN proteins, namely in CENPA (Cid), MIS12 (Mis12, Nnf1a, Nnf1b), KNL1 (Spc105R), and NDC80 (Ndc80 and Spc25), have been shown to impact synapse formation in the neuromuscular junction [59,85].

While conditional deletion of the core **anaphase-promoting complex/cyclosome** (**APC/C**) component APC4 does not affect synaptogenesis of cortical mouse neurons, CDC20 deletion promoted presynaptic differentiation in primary post-mitotic mammalian neurons and the rat cerebellar cortex [54,86]. Furthermore, CDC20 mediated the degradation of neuronal differentiation 2 (NEUROD2) [86]. The apparent discrepancies in the results related to different APC/C members may reflect context-dependent or function/dependent complexity, rather than true contradictions. For instance, in the mitotic context of non-neuronal cells, alternative CDC20 isoform ratios control differently mitotic arrest duration [87]. These findings open novel directions for investigating possible APC/C-independent roles of CDC20 function within the neuronal context. This example underlines the importance of analysing mitotic proteins individually rather than exclusively as components of canonical pathways.

So far, the roles of mitotic proteins in neuronal structure and function – from migration to dendritic development and synapse formation – are individually well supported by mechanistic evidence. Further studies are required to help clarify whether findings can be extrapolated to other contexts, for instance, by assuming that proteins that belong to the same pathway exert identical functions.

The integration of mitotic proteins into pathway-based mechanisms or neuronal circuits is only beginning to emerge. The Wnt signalling pathway arises as an important pathway connecting mitotic proteins and neuronal functions [88–90]. On the one hand, Wnt signalling peaks during mitosis, where it regulates mitotic progression, asymmetric cell division, spindle dynamics, and

chromosome segregation. On the other hand, its gradients govern key processes such as axon pathfinding, neuronal survival, migration, and the assembly and distribution of synapses at later stages – all essential steps in assembling complex neuronal circuits [88,90,91]. During mitosis, in non-neuronal contexts, Wnt signalling modulates KIF2A activity and localisation at the spindle poles to ensure timely chromosome alignment [92]. Also, KIF2A plays critical roles in post-mitotic neurons as discussed earlier. Considering KIF2A non-neuronal context roles, it would be important to study whether Wnt modulates KIF2A's functions in the neuronal context. Interestingly, in humans, KIF2A mutations are associated with a variety of cortical malformations, epilepsy, autism spectrum disorder, and neurodegeneration [93].

Impact of mitotic proteins on brain pathologies

Mitotic proteins in neurodevelopmental disorders

The probably most well-established connection between mitotic proteins and brain disease is in the aetiology of primary microcephaly. Primary microcephaly can arise from genetic causes and environmental factors (e.g., Zika virus infection) [5,11,94]. Most microcephaly-associated mutations are in genes encoding proteins involved in centrosome duplication, **kinetochore** assembly, microtubule dynamics, and chromosome structure, all essential for proper cell division. These are linked with MCPH (mutations in 30 genes), Seckel syndrome (SCKL, two genes), microcephalic osteodysplastic primordial dwarfism type II (MOPDII, one gene), mosaic variegated aneuploidy (MVA, three genes), and cohesinopathies (three genes) [5,11,16,17]. The crosstalk of mitotic process and primary microcephaly is further supported by proteomic analyses showing that Zika virus infection alters the levels of proteins involved in cell proliferation [94]. Zika virus infection induces mitotic abnormalities and chromosome mis-segregation, implicating mitotic proteins in its microcephaly-associated pathogenic mechanisms [94,95]. The link between mitotic protein dysfunction and brain development has also been documented in several experimental models. For instance, inflicting a temporal aneuploidy status during *Drosophila* development leads to defects solely in the brain of the adult fly [96]. Similarly, extending the duration of the G1 cell cycle phase through cyclin-dependent kinase (CDK) activity downregulation was sufficient to induce neuronal differentiation in whole-embryo mouse cultures [97]; and cell cycle progression delays induced by microtubule depolymerisation drugs in mice resulted in microcephaly [98]. These findings stress that the brain is especially vulnerable to mitotic disruption and support a mechanistic link between mitotic protein dysfunction and microcephaly.

Current models largely focus on the dysfunctional 'classical' roles of mitotic proteins, including in the mitotic spindle orientation, **cleavage plane orientation**, or mitotic timing [5,16,17]. Mitotic delays can result from mitotic errors, such as defective spindle assembly or chromosome alignment problems; if unresolved, these errors can lead to chromosome mis-segregation and ultimately result in aneuploidy [15]. A common framework behind of these mechanisms is the radial unit hypothesis, which implies that the onset and frequency of asymmetric divisions directly impact the self-renewal capacity of NPCs and, consequently, the number of generated neurons, cortical expansion and neocortex size [5,17,99]. However, in the context of mitotic proteins, current perspectives often overlook the non-canonical functions of these proteins, which may also critically perturb neuronal generation and maintenance.

Although less explored, the dual role in cell division and neuronal function can also be observed in the context of TRAPPopathies. TRAPPopathies are caused by pathogenic variants in genes encoding trafficking protein particle (TRAPP) subunits, involved in vesicular transport between intracellular compartments. This group of disorders is characterised by a spectrum of neurological defects, ranging from microcephaly and epilepsy to muscular dystrophy and intellectual disability [100]. TRAPP complex subunit 4 (TRAPPC4, also known as Synbindin) participates in

postsynaptic membrane trafficking, and evidence from cancer cells indicates that it supports proliferation through its association with the Ras–Raf–MEK–ERK signalling cascade [101–103]. This pathway has been extensively studied for its roles in cell cycle progression, neuronal differentiation and synaptic function [100]. Similarly, TRAMM (TRAPPC12), another TRAPP subunit, is essential for kinetochore integrity and the recruitment of the centromere-associated protein E (CENPE) [100,104]. Although being discovered as TRAPP subunits, these two proteins are functionally linked to mitosis, providing compelling evidence that mitotic regulators may contribute to neurodevelopmental disorders through canonical and non-canonical mechanisms.

Importantly, despite strong evidence from both mouse and human studies supporting the impact of defective mitosis on neurogenesis, the contribution of mitotic dysfunction to the pathogenic mechanisms of many proteins is still inferred from studies in non-neuronal contexts [5,19]. Organoid models carrying patient-associated mutations contributed to uncovering mechanisms that deregulate neural stem cell proliferation, maintenance, and differentiation [105,106]. However, the limited capacity of such platforms to model human cortical expansion constrains research on non-canonical roles of mitotic proteins in neurodevelopmental disorders.

Mitotic proteins in neurodegenerative disorders

The controversy surrounding mitotic proteins in neurodegenerative disorders primarily focuses on the extent of their direct influence on the neurodegenerative pathways. One well-supported mechanism that may contribute to neuronal loss involves neuronal aneuploidy/chromosomal instability and aberrant re-entry into the cell cycle [23,25,26,107–109], specifically in Alzheimer's disease (AD), Huntington's disease (HD), and frontotemporal dementia (FTD) [8,23,25,110]. The roles of cyclins and CDKs in these processes are well-established [9,111]. Shugoshin-1 (SGO1), a key protector of cohesin during the process of mitosis, has been directly linked to AD pathology through aneuploidy [112,113]. *Sgo1* heterozygous mice, a model of chromosomal instability, spontaneously exhibited hallmark AD features, including amyloid-β accumulation originating from phospho-Histone3-positive mitotic cells with prolonged mitotic activity [112]. Conditional deletion of the cohesin subunit RAD21 in post-mitotic neurons disrupts neuronal gene expression programs, impairs proper maturation and cortical neuron activation [114]. As described in the preceding text, the SMC3 subunit is also required for proper dendritic morphology and synapses [35,53]. Together, these findings support that cohesin dysfunction contributes to AD pathology, with SGO1 acting via its mitotic function and RAD21 and SMC3 – both components of the cohesin complex – through their non-mitotic roles in neurons. However, it is important to mention that chromosomal instability on its own does not appear to be sufficient to cause the AD pathology, as *BubR1* heterozygous mice, another chromosomal instability model, fail to exhibit amyloid-β accumulation over time [113].

Mitochondrial dysfunction has been implicated in the pathogenesis of almost all neurodegenerative diseases. This includes AD, although it remains unclear whether mitochondrial dysfunction is a primary cause or a consequence of the disease progression [115,116]. Recent studies show that, during mitosis, actin regulates the balanced distribution of the mitochondrial network in human cells [117]. The subcortical actin cables, assembled in the mitotic cytoplasm, organise three-dimensional mitochondrial positioning to ensure equal segregation of healthy mitochondria during cytokinesis. Interestingly, mitochondrial genetic drift through mitotic segregation plays a role in ageing and the timing of neurogenesis [99,118].

Emerging research highlights signalling pathways shared between neurodevelopment and neurodegenerative disorders. Wnt signalling alteration has been reported in the pathogenesis of HD, AD, PD, and amyotrophic lateral sclerosis (ALS) [89]. Many other signalling pathways have been

proposed to be dysregulated in AD, including transforming growth factor (TGF)-β, p53, mammalian target of rapamycin (mTOR), NF-κB, and PI3K/AKT signalling [119]. Whether mitotic proteins contribute to this mechanistic link between neurodevelopmental and neurodegenerative disorders remains highly speculative. In addition to Wnt signalling, which regulates several aspects of mitosis (see earlier), other important neuronal signalling pathways are also interconnected with mitotic proteins. For instance, PI3K/AKT signalling is critical for mitotic spindle assembly, and kinetochore components are known to modulate TNFα-induced NF-κB activation [120,121]. More recently, p53 has been linked with pathomechanisms in MCPH and MVA mitotic-associated genes [17,122,123]. Understanding how these signalling pathways contribute to neurodegenerative diseases may elucidate the role of mitotic proteins in neurodegenerative aetiology.

Amyloid precursor protein (APP), while mostly concentrated in the neuronal synapses in the adult nervous system, is broadly expressed during nervous system development. There, as shown in mouse studies, it balances the progenitor and neurogenic state of NPCs and facilitates canonical Wnt signalling [124]. Similarly, Huntingtin overexpression inhibits cell division in both *Drosophila* and mouse models [125,126]. This evidence suggests that the early phases of HD involve slow and progressive disruptions in normal neurodevelopment that eventually transition into neurodegeneration. Also, reduced adult neurogenesis significantly contributes to the progression of neurodegenerative diseases, further highlighting the complex interplay between developmental and degenerative pathways and mitotic and post-mitotic processes [3,19,111,126].

Concluding remarks

Mitotic proteins remain expressed in the adult brain under physiological conditions, particularly in cortical neurons (Figure 1). Here, we have summarised how mutations and alterations in mitotic protein expression affect post-mitotic functions in cortical neurons. We have also reviewed emerging perspectives on the non-mitotic roles of mitotic proteins, highlighting how their dysfunction contributes to pathological mechanisms in both neurodevelopmental and neurodegenerative disorders.

So far, non-canonical functional studies have been conducted for only a limited number of mitotic proteins, and whether the principles revealed in these studies hold for other proteins remains to be seen [4,9,18,59]. Multi-omics datasets, including genomics, transcriptomics, proteomics, and epigenomics, are starting to reveal the identification of novel mitotic proteins in physiological and pathological neuronal contexts [1–14,93]. Future research is essential to elucidate the contribution of these mitotic proteins in post-mitotic neurons. Among the focus areas for future research are processes such as neuronal differentiation, migration, polarisation, dendritic arbour elaboration, and synaptic plasticity, which are fundamental to the initial formation of neural circuits during early brain development [28].

Research should also expand to explore the involvement of mitotic proteins in specific signalling pathways – for instance the Wnt pathway – and their roles in neural circuit formation, development, and plasticity. Similar to KIFs' role in microtubule dynamics in neurons, specific pathways mediated by mitotic proteins (e.g., at kinetochores) may emerge as critical players in shaping post-mitotic neuronal networks [18,77]. This understanding will be critical for dissecting non-canonical roles of mitotic proteins (see Outstanding questions) in the aetiology of neurodevelopmental and neurodegenerative diseases, beyond their established functions in cell division [16,17]. However, conventional methods such as overexpression, knockout, or knockdown affect multiple functions simultaneously, making it difficult to distinguish the specific contributions of canonical and non-canonical roles of mitotic proteins to brain function. This is particularly important in the context of neurodevelopmental disorders, where species-specific

Outstanding questions

How do non-canonical functions of mitotic proteins vary across neuronal subtypes and brain regions? Are these functions conserved, or do they exhibit cell-type and region-specific regulation?

Which molecular pathways regulate mitotic proteins during development and in mature neurons? How are mitotic proteins localized in specific neuronal compartments, and how do they affect neuronal function and plasticity? Do they follow developmental cues or mechanisms shared with mitosis?

How do mitotic proteins contribute to neurodevelopmental and neurodegenerative disorders? Do they share common pathogenic mechanisms or act through distinct pathways?

Can the study of mitotic proteins in mature neurons uncover novel paradigms for understanding how they contribute to shaping neuronal circuit structure and function in the human brain?

Can the non-canonical functions of mitotic proteins yield novel therapeutic strategies and reliable biomarkers for neurodevelopmental and neurodegenerative disorders? Are mitotic pathway-targeting drugs viable candidates for repurposing?

differences in the expansion of the outer subventricular zone may constrain the repertoire of mitotic proteins in post-mitotic functions [19,99].

While this review focused mostly on the cerebral cortex, mitotic proteins also hold non-mitotic functions in other brain regions. For instance, in hippocampal neurons, KIF2C controls spine morphology [58]. Polo-like kinase 2 (PLK2), beyond its mitotic centrosome duplication roles, is essential for synaptic scaling in hippocampal neurons, and *Plk2* was found to be upregulated in the hippocampus of a PD mouse model [127–129]. *BubR1* insufficiency is associated with *in vitro* reduced hypomyelination, decreased expression of key oligodendrocyte differentiation genes, and altered motor function [130]. As such, research should extend to other brain areas and neural cell types, such as astrocytes and oligodendrocytes.

Expanding the investigation of mitotic proteins' non-canonical functions in more complex physiological settings can offer insights into the molecular mechanisms of neural development and its maintenance processes. However, a current major challenge lies in validating these findings and integrating them into the complexity of neuronal diversity and functional circuitry [28]. It will be important to ascertain in which specific cell types mitotic proteins act, and whether mitotic protein dysfunction exhibits predominant effects in certain cell types or acts broadly across neural populations. Emerging data from multi-omics studies should help to dissect these patterns. This research will stimulate the identification of novel biomarkers and the development of new therapeutic approaches. Existing drugs that modulate mitotic pathways could be repurposed – for instance, from the cancer field – offering innovative strategies for treating neurological conditions [110]. Future clinical trials should assess drugs' blood–brain barrier penetration, toxicity, and efficacy in neurological contexts, which remain largely unexplored [131]. Altogether, these efforts will contribute to redefine mitotic proteins' roles by expanding research beyond their **canonical functions** to include functions in neurons and other cell types. This will offer an opportunity to deepen our understanding of how regulators of chromosome segregation shape brain development, maintenance, and homeostasis.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Grammarly and ChatGPT for grammar checking. The authors take full responsibility for the content of the publication.

Acknowledgments

We thank Soraia Barão and the laboratory for insightful discussions. This work was supported by Fundação para a Ciência e Tecnologia (FCT): CEECIND/03721/2018/CP1540/CT0003, (DOI 10.54499/CEECIND/03721/2018/CP1540/CT0003); 2022.01028.PTDC (DOI 10.54499/2022.01028.PTDC), and Prémio de investigação translacional João Larguito: NeuRARE – Development of a pipeline into unravelling the molecular and cellular basis of rare neurologic diseases supported by AD-ABC Funds.

Declaration of interests

S.C. declares no competing interests. J.C. is an employee of CANNPRISMA.

References

1. Nehme, R. *et al.* (2024) Genomic, molecular, and cellular divergence of the human brain. *Trends Neurosci.* 47, 491–505
2. Piwecka, M. *et al.* (2023) Single-cell and spatial transcriptomics: deciphering brain complexity in health and disease. *Nat. Rev. Neurol.* 19, 346–362
3. Li, J. *et al.* (2025) Multimodal insights into adult neurogenesis: an integrative review of multi-omics approaches. *Heliyon* 11, e42668
4. Akagawa, R. *et al.* (2021) Alternative functions of cell cycle-related and DNA repair proteins in post-mitotic neurons. *Front. Cell Dev. Biol.* 9, 753175
5. Asif, M. *et al.* (2023) Congenital microcephaly: a debate on diagnostic challenges and etiological paradigm of the shift from isolated/non-syndromic to syndromic microcephaly. *Cells* 12, 642
6. Jang, Y. *et al.* (2023) Mass spectrometry–based proteomics analysis of human substantia nigra from Parkinson's disease patients identifies multiple pathways potentially involved in the disease. *Mol. Cell. Proteomics* 22, 100452
7. Jean, F. *et al.* (2020) Dissecting the genetic and etiological causes of primary microcephaly. *Front. Neurol.* 11, 570830

8. Joseph, C. *et al.* (2020) Cell cycle deficits in neurodegenerative disorders: uncovering molecular mechanisms to drive innovative therapeutic development. *Aging Dis.* 11, 946–966
9. Marlier, Q. *et al.* (2020) Core cell cycle machinery is crucially involved in both life and death of post-mitotic neurons. *Cell. Mol. Life Sci.* 77, 4553–4571
10. Toupenet Marchesi, L. *et al.* (2025) Transcriptomic analysis reinforces the implication of spatacsin in neuroinflammation and neurodevelopment. *Sci. Rep.* 15, 2370
11. Carvalhal, S. *et al.* (2022) Biallelic BUB1 mutations cause microcephaly, developmental delay, and variable effects on cohesion and chromosome segregation. *Sci. Adv.* 8, eabk0114
12. Barão, S. *et al.* (2024) Conserved transcriptional regulation by BRN1 and BRN2 in neocortical progenitors drives mammalian neural specification and neocortical expansion. *Nat. Commun.* 15, 8043
13. Ibrayeva, A. *et al.* (2021) Early stem cell aging in the mature brain. *Cell Stem Cell* 28, 955–966.e7
14. Li, K.W. *et al.* (2020) Recent developments in data independent acquisition (DIA) mass spectrometry: application of quantitative analysis of the brain proteome. *Front. Mol. Neurosci.* 13, 564446
15. Maiato, H. and Silva, S. (2023) Double-checking chromosome segregation. *J. Cell Biol.* 222, e202301106
16. Eronique Marthiens, V. *et al.* (2020) Centrosomes: the good and the bad for brain development. *Biol. Cell.* 112, 153–172
17. Phan, T.P. and Holland, A.J. (2021) Time is of the essence: the molecular mechanisms of primary microcephaly. *Genes Dev.* 35, 1551–1578
18. Joseph, N.F. *et al.* (2021) Double duty: mitotic kinesins and their post-mitotic functions in neurons. *Cells* 10, 1–11
19. Kalebic, N. and Huttner, W.B. (2020) Basal progenitor morphology and neocortex evolution. *Trends Neurosci.* 43, 843–853
20. Huilgol, D. *et al.* (2023) Direct and indirect neurogenesis generate a mosaic of distinct glutamatergic projection neuron types in cerebral cortex. *Neuron* 111, 2557–2569.e4
21. Clément, F. and Olayé, J. (2024) A stochastic model for neural progenitor dynamics in the mouse cerebral cortex. *Math. Biosci.* 372, 109185
22. Guo, D. *et al.* (2024) Significance of programmed cell death pathways in neurodegenerative diseases. *Int. J. Mol. Sci.* 25, 9947
23. Albert, O. *et al.* (2023) Chromosome instability and aneuploidy in the mammalian brain. *Chromosom. Res.* 31, 32
24. Milagre, I. *et al.* (2023) Compromised mitotic fidelity in human pluripotent stem cells. *Int. J. Mol. Sci.* 24, 11933
25. Islam, A. *et al.* (2024) Aneuploidy is linked to neurological phenotypes through oxidative stress. *J. Mol. Neurosci.* 74, 50
26. Iourov, I.Y. *et al.* (2021) Chromosome instability, aging and brain diseases. *Cells* 10, 1256
27. Baker, N.E. and Montagna, C. (2022) Reducing the aneuploid cell burden – cell competition and the ribosome connection. *Dis. Model. Mech.* 15, dmm049673
28. Luo, L. (2021) Architectures of neuronal circuits. *Science* 373, eabg7285
29. Akter, M. *et al.* (2021) Neurogenesis and neuronal migration in the postnatal ventricular-subventricular zone: similarities and dissimilarities between rodents and primates. *Neurosci. Res.* 167, 64–69
30. Hatanaka, Y. and Hirata, T. (2020) How do cortical excitatory neurons terminate their migration at the right place? Critical roles of environmental elements. *Front. Cell Dev. Biol.* 8, 596708
31. Nakajima, C. *et al.* (2021) Postnatal neuronal migration in health and disease. *Curr. Opin. Neurobiol.* 66, 1–9
32. Wu, N. *et al.* (2024) Research advances in neuroblast migration in traumatic brain injury. *Mol. Neurobiol.* 61, 1–13
33. Meneses Iack, P. *et al.* (2022) Microcephaly gene Cenpj regulates axonal growth in cortical neurons through microtubule destabilization. *J. Neurochem.* 161, 320–334
34. Van Den Berg, D.L.C. *et al.* (2017) Nipbl interacts with zfp609 and the integrator complex to regulate cortical neuron migration. *Neuron* 93, 348–361
35. Alonso-Gil, D. and Losada, A. (2023) NIPBL and cohesin: new take on a classic tale. *Trends Cell Biol.* 33, 860–871
36. Cunha-Ferreira, I. *et al.* (2018) The HAUS complex is a key regulator of non-centrosomal microtubule organization during neuronal development. *Cell Rep.* 24, 791–800
37. Kraus, J. *et al.* (2023) Microtubule nucleation for spindle assembly: one molecule at a time. *Trends Biochem. Sci.* 48, 761–775
38. Wu, X. *et al.* (2023) The neurological and non-neurological roles of the primary microcephaly-associated protein ASPM. *Front. Neurosci.* 17, 1242448
39. Ferreira, S.L. *et al.* (2024) Homozygous variant on CLASP2 gene associated to intellectual disability and rhythm disorder. *SciBase Cardiol.* 2, 1006
40. Jossin, Y. (2020) Reelin functions, mechanisms of action and signaling pathways during brain development and maturation. *Biomolecules* 10, 964
41. Lawrence, E.J. *et al.* (2020) CLASPs at a glance. *J. Cell Sci.* 133, jcs243097
42. Dillon, G.M. *et al.* (2017) CLASP2 Links reelin to the cytoskeleton during neocortical development. *Neuron* 93, 1344–1358.e5
43. Rodgers, N.C. *et al.* (2023) CLASP2 facilitates dynamic actin filament organization along the microtubule lattice. *Mol. Biol. Cell* 34, br3
44. Molnár, Z. *et al.* (2020) Transient cortical circuits match spontaneous and sensory driven activity during development. *Science* 370, eabb2153
45. Muralidharan, H. and Baas, P.W. (2019) Mitotic motor KIFC1 is an organizer of microtubules in the axon. *J. Neurosci.* 39, 3792–3811
46. Muralidharan, H. *et al.* (2022) KIFC1 Regulates the trajectory of neuronal migration. *J. Neurosci.* 42, 2149–2165
47. Ngo, L. *et al.* (2014) TUBB5 and its disease-associated mutations influence the terminal differentiation and dendritic spine densities of cerebral cortical neurons. *Hum. Mol. Genet.* 23, 5147–5158
48. Madrigal, I. *et al.* (2019) Spectrum of clinical heterogeneity of β-tubulin *TUBB5* gene mutations. *Gene* 695, 12–17
49. Willemsen, M.H. *et al.* (2012) Mutations in *DYNC1H1* cause severe intellectual disability with neuronal migration defects. *J. Med. Genet.* 49, 179–183
50. Möller, B. *et al.* (2024) The expanding clinical and genetic spectrum of DYNC1H1-related disorders. *Brain* 148, 597–612
51. Zombor, M. *et al.* (2019) A novel WDR62 missense mutation in microcephaly with abnormal cortical architecture and review of the literature. *J. Appl. Genet.* 60, 151–162
52. Shohayeb, B. *et al.* (2020) The spindle-associated microcephaly protein, WDR62, is required for neurogenesis and development of the hippocampus. *Front. Cell Dev. Biol.* 8, 549353
53. Fujita, Y. *et al.* (2017) Decreased cohesin in the brain leads to defective synapse development and anxiety-related behavior. *J. Exp. Med.* 214, 1431–1452
54. Day, J.L. *et al.* (2024) Deletion of a core APC/C component reveals APC/C function in regulating neuronal USP1 levels and morphology. *Front. Mol. Neurosci.* 17, 1352782
55. Joseph, N.F. *et al.* (2020) Molecular Motor KIF3B Acts as a key regulator of dendritic architecture in cortical neurons. *Front. Cell. Neurosci.* 14, 521199
56. Wan, Y. *et al.* (2022) KIF4 regulates neuronal morphology and seizure susceptibility via the PARP1 signaling pathway. *J. Cell Biol.* 222, e202208108
57. Midorikawa, R. *et al.* (2006) KIF4 motor regulates activity-dependent neuronal survival by suppressing PARP-1 enzymatic activity. *Cell* 125, 371–383
58. Zheng, R. *et al.* (2022) KIF2C regulates synaptic plasticity and cognition in mice through dynamic microtubule depolymerization. *eLife* 11, e72483
59. Zhao, G. *et al.* (2019) Kinetochore proteins have a post-mitotic function in neurodevelopment. *Dev. Cell* 48, 873–882.e4
60. Alves Domingos, H. *et al.* (2025) The kinetochore protein KNL-1 regulates the actin cytoskeleton to control dendrite branching. *J. Cell Biol.* 224, e202311147
61. Meka, D.P. *et al.* (2022) Centrosome-dependent microtubule modifications set the conditions for axon formation. *Cell Rep.* 39, 110686
62. De Anda, F.C. *et al.* (2010) Centrosome motility is essential for initial axon formation in the neocortex. *J. Neurosci.* 30, 10391–10406
63. Gwee, S.S.L. *et al.* (2018) Aurora kinase B regulates axonal outgrowth and regeneration in the spinal motor neurons of developing zebrafish. *Cell. Mol. Life Sci.* 75, 4269–4285

64. Ledvin, L. *et al.* (2023) The anaphase-promoting complex controls a ubiquitination-phosphoprotein axis in chromatin during neurodevelopment. *Dev. Cell* 58, 2666–2683.e9
65. Nwagbara, B.U. *et al.* (2014) TACC3 is a microtubule plus end–tracking protein that promotes axon elongation and also regulates microtubule plus end dynamics in multiple embryonic cell types. *MBoC* 25, 3350–3362
66. Erdogan, B. *et al.* (2020) Investigating the impact of the phosphorylation status of tyrosine residues within the TACC domain of TACC3 on microtubule behavior during axon growth and guidance. *Cytoskeleton* 77, 277–291
67. Erdogan, B. *et al.* (2017) The microtubule plus-end-tracking protein TACC3 promotes persistent axon outgrowth and mediates responses to axon guidance signals during development. *Neural Dev.* 12, 3
68. Kahn, O.I. *et al.* (2015) TPX 2 regulates neuronal morphology through kinesin-5 interaction. *Cytoskeleton* 72, 340–348
69. Chen, Y.-J. *et al.* (2024) The non-mitotic role of HMMR in regulating the localization of TPX2 and the dynamics of microtubules in neurons. *eLife* 13, RP94547
70. Xiong, G.-J. and Sheng, Z.-H. (2024) Presynaptic perspective: axonal transport defects in neurodevelopmental disorders. *J. Cell Biol.* 223, e202401145
71. Cason, S.E. and Holzbaur, E.L.F. (2022) Selective motor activation in organelle transport along axons. *Nat. Rev. Mol. Cell Biol.* 23, 699–714
72. Gomes Paim, L.M. and Bechstedt, S. (2025) Regulation of microtubule growth rates and their impact on chromosomal instability. *Cell Cycle* 22, 1–20
73. Sleigh, J.N. *et al.* (2019) Axonal transport and neurological disease. *Nat. Rev. Neurol.* 15, 691–703
74. Guillaud, L. *et al.* (2020) Anterograde axonal transport in neuronal homeostasis and disease. *Front. Mol. Neurosci.* 13, 556175
75. Ricci, A. *et al.* (2024) Eg5 and diseases: from the well-known role in cancer to the less-known activity in noncancerous pathological conditions. *Biochem. Res. Int.* 2024, 3649912
76. Myers, K.A. and Baas, P.W. (2007) Kinesin-5 regulates the growth of the axon by acting as a brake on its microtubule array. *J. Cell Biol.* 178, 1081–1091
77. Swarnkar, S. *et al.* (2018) Kinesin family of proteins Kif11 and Kif21B act as inhibitory constraints of excitatory synaptic transmission through distinct mechanisms. *Sci. Rep.* 8, 17419
78. Lu, W. *et al.* (2025) 'Mitotic' kinesin-5 is a dynamic brake for axonal growth in *Drosophila*. *Development* 152, dev204424
79. Tekin, H.G. *et al.* (2022) Spinal muscular atrophy with predominant lower extremity (SMA-LED) with no signs other than pure motor symptoms at the intersection of multiple overlap syndrome. *Brain Dev* 44, 294–298
80. Romero, D.M. *et al.* (2023) A human dynein heavy chain mutation impacts cortical progenitor cells causing developmental defects, reduced brain size and altered brain architecture. *Neurobiol. Dis.* 180, 106085
81. Fellows, A.D. *et al.* (2024) Dynein and dynactin move long-range but are delivered separately to the axon tip. *J. Cell Biol.* 223, e202309084
82. Nirschl, J.J. *et al.* (2016) α-Tubulin tyrosination and CLIP-170 phosphorylation regulate the initiation of dynein-driven transport in neurons. *Cell Rep.* 14, 2637–2652
83. Breuss, M. *et al.* (2016) Mutations in the murine homologue of TUBB5 cause microcephaly by perturbing cell cycle progression and inducing p53-associated apoptosis. *Development* 143, 1126–1133
84. Beffert, U. *et al.* (2012) Microtubule plus-end tracking protein CLASP2 regulates neuronal polarity and synaptic function. *J. Neurosci.* 32, 13906–13916
85. Cheerambathur, D.K. *et al.* (2019) The kinetochore-microtubule coupling machinery is repurposed in sensory nervous system morphogenesis. *Dev. Cell* 48, 864–872.e7
86. Yang, Y. *et al.* (2009) A Cdc20-APC ubiquitin signaling pathway regulates presynaptic differentiation. *Science* 326, 575–578
87. Tsang, M.-J. and Cheeseman, I.M. (2023) Alternative CDC20 translational isoforms tune mitotic arrest duration. *Nature* 617, 154–161
88. Da Silva, F. *et al.* (2021) Mitotic WNT signalling orchestrates neurogenesis in the developing neocortex. *EMBO J.* 40, e108041
89. Ramakrishna, K. *et al.* (2023) WNT-β catenin signaling as a potential therapeutic target for neurodegenerative diseases: current status and future perspective. *Diseases* 11, 89
90. Teo, S. and Salinas, P.C. (2021) Wnt-frizzled signaling regulates activity-mediated synapse formation. *Front. Mol. Neurosci.* 14, 683035
91. Habib, S.J. and Acebrón, S.P. (2022) Wnt signalling in cell division: from mechanisms to tissue engineering. *Trends Cell Biol.* 32, 1035–1048
92. Bufe, A. *et al.* (2021) Wnt signaling recruits KIF2A to the spindle to ensure chromosome congression and alignment during mitosis. *Proc. Natl. Acad. Sci. U. S. A.* 118, e2108145118
93. Ruiz-Reig, N. *et al.* (2023) Connecting neurodevelopment to neurodegeneration: a spotlight on the role of kinesin superfamily protein 2A (KIF2A). *Neural Regen. Res.* 19, 375–379
94. Rosa-Fernandes, L. *et al.* (2022) The impact of Zika virus exposure on the placental proteomic profile. *Biochim. Biophys. Acta (BBA) - Mol. Basis Dis.* 1868, 166270
95. Giraldo, M.I. *et al.* (2023) Pathogenesis of Zika virus infection. *Annu. Rev. Pathol.* 18, 181–203
96. Mirkovic, M. *et al.* (2019) Induced aneuploidy in neural stem cells triggers a delayed stress response and impairs adult life span in flies. *PLoS Biol.* 17, e3000016
97. Calegari, F. and Huttner, W.B. (2003) An inhibition of cyclin-dependent kinases that lengthens, but does not arrest, neuroepithelial cell cycle induces premature neurogenesis. *J. Cell Sci.* 116, 4947–4955
98. Mitchell-Dick, A. *et al.* (2019) Acute lengthening of progenitor mitosis influences progeny fate during cortical development *in vivo*. *Dev. Neurosci.* 41, 300–317
99. Aquilino, M. *et al.* (2025) Epigenetic and metabolic regulation of developmental timing in neocortex evolution. *Trends Neurosci.* 27, 27:S0166-2236(25)00056-6
100. Hall, R. *et al.* (2024) TRAPPopathies: severe multisystem disorders caused by variants in genes of the transport protein particle (TRAPP) complexes. *Int. J. Mol. Sci.* 25, 13329
101. Kong, X. *et al.* (2013) Synbindin in extracellular signal-regulated protein kinase spatial regulation and gastric cancer aggressiveness. *J. Natl. Cancer Inst.* 105, 1738–1749
102. Zhao, S.-L. *et al.* (2011) TRAPPC4-ERK2 interaction activates ERK1/2, modulates its nuclear localization and regulates proliferation and apoptosis of colorectal cancer cells. *PLoS One* 6, e23262
103. Ethell, I.M. *et al.* (2000) Synbindin, a novel syndecan-2-binding protein in neuronal dendritic spines. *J. Cell Biol.* 151, 53–68
104. Milev, M.P. *et al.* (2015) TRAMM/TrappC12 plays a role in chromosome congression, kinetochore stability, and CENP-E recruitment. *J. Cell Biol.* 209, 221–234
105. Gabriel, E. *et al.* (2020) Human brain organoids to decode mechanisms of microcephaly. *Front. Cell. Neurosci.* 14, 115
106. Winden, K.D. *et al.* (2025) Using cortical organoids to understand the pathogenesis of malformations of cortical development. *Front. Neurosci.* 18, 1522652
107. Zekanowski, C. and Wojda, U. (2009) Aneuploidy, chromosomal missegregation, and cell cycle reentry in Alzheimer's disease. *Acta Neurobiol. Exp.* 69, 232–253
108. Rehen, S.K. *et al.* (2005) Constitutional aneuploidy in the normal human brain. *J. Neurosci.* 25, 2176–2180
109. Yurov, Y.B. *et al.* (2019) Chromosome instability in the neurodegenerating brain. *Front. Genet.* 10, 892
110. Lui, A. *et al.* (2022) FDA-Approved kinase inhibitors in preclinical and clinical trials for neurological disorders. *Pharmaceuticals (Basel)* 15, 1546
111. Advani, D. and Kumar, P. (2024) Uncovering cell cycle dysregulations and associated mechanisms in cancer and neurodegenerative disorders: a glimpse of hope for repurposed drugs. *Mol. Neurobiol.* 61, 8600–8630
112. Rao, C.V. *et al.* (2020) GSK3-ARC/Arg3.1 and GSK3-Wnt signaling axes trigger amyloid-β accumulation and neuroinflammation in middle-aged Shugoshin 1 mice. *Aging Cell* 19, e13221
113. Rao, C.V. *et al.* (2018) Spontaneous development of Alzheimer's disease-associated brain pathology in a Shugoshin-1 mouse cohesinopathy model. *Aging Cell* 17, e12797

114. Weiss, F.D. *et al.* (2021) Neuronal genes deregulated in Cornelia de Lange syndrome respond to removal and re-expression of cohesin. *Nat. Commun.* 12, 2919
115. Bhatia, S. *et al.* (2022) Mitochondrial dysfunction in Alzheimer's disease: opportunities for drug development. *Curr. Neuropharmacol.* 20, 675–692
116. Calvo-Rodriguez, M. and Bacskai, B.J. (2021) Mitochondria and calcium in Alzheimer's disease: from cell signaling to neuronal cell death. *Trends Neurosci.* 44, 136–151
117. Moore, A.S. *et al.* (2021) Actin cables and comet tails organize mitochondrial networks in mitosis. *Nature* 591, 659–664
118. Smith, A.L.M. *et al.* (2022) Mitochondrial DNA mutations in ageing and cancer. *Mol. Oncol.* 16, 3276–3294
119. Soelter, T.M. *et al.* (2024) Altered glia-neuron communication in Alzheimer's disease affects WNT, p53, and NFkB signaling determined by snRNA-seq. *Cell Commun. Signal.* 22, 317
120. Deng, S. *et al.* (2022) PI3K/AKT signaling tips the balance of cytoskeletal forces for cancer progression. *Cancers (Basel)* 14, 1652
121. Morgan, E.L. *et al.* (2024) Functional RNAi screening identifies G2/M and kinetochore components as modulators of TNFα/NF-κB prosurvival signaling in head and neck squamous cell carcinoma. *Cancer Res. Commun.* 4, 2903–2918
122. Sterling, N.A. *et al.* (2023) P53 independent pathogenic mechanisms contribute to BubR1 microcephaly. *Front. Cell Dev. Biol.* 11, 1282182
123. Iegiani, G. *et al.* (2023) The impact of TP53 activation and apoptosis in primary hereditary microcephaly. *Front. Neurosci.* 17, 1220010
124. Shabani, K. *et al.* (2023) The temporal balance between self-renewal and differentiation of human neural stem cells requires the amyloid precursor protein. *Science. Advances* 9, eadd5002
125. Dubey, S.K. *et al.* (2024) Disrupted nuclear import of cell cycle proteins in Huntington's/PolyQ disease causes neurodevelopment defects in cellular and *Drosophila* model. *Heliyon* 10, e26393
126. Barnat, M. *et al.* (2020) Huntington's disease alters human neurodevelopment. *Science* 369, 787–793
127. Seeburg, D.P. *et al.* (2008) Critical role of CDK5 and polo-like kinase 2 in homeostatic synaptic plasticity during elevated activity. *Neuron* 58, 571–583
128. Jia, E. *et al.* (2023) Spatial transcriptome profiling of mouse hippocampal single cell microzone in Parkinson's disease. *Int. J. Mol. Sci.* 24, 1810
129. Zhang, C. *et al.* (2022) Polo-like kinase 2: from principle to practice. *Front. Oncol.* 12, 956225
130. Choi, C.-I. *et al.* (2016) The progeroid gene BubR1 regulates axon myelination and motor function. *Aging* 8, 2667–2688
131. González-Martínez, J. *et al.* (2022) Genetic interaction between PLK1 and downstream MCPH proteins in the control of centrosome asymmetry and cell fate during neural progenitor division. *Cell Death Differ.* 29, 1474–1485
132. Zhang, C. *et al.* (2020) Distinct roles of TRAPPC8 and TRAPPC12 in ciliogenesis via their interactions with OFD1. *Front. Cell Dev. Biol.* 8, 148
133. Saatci, O. *et al.* (2023) Targeting TACC3 represents a novel vulnerability in highly aggressive breast cancers with centrosome amplification. *Cell Death Differ.* 30, 1305–1319