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## Alternative functions of core cell cycle regulators in neuronal migration, neuronal maturation, and synaptic plasticity

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### Abstract

Recent studies have demonstrated that boundaries separating a cycling cell from a post-mitotic neuron are not as concrete as expected. Novel and unique physiological functions in neurons have been ascribed for proteins fundamentally required for cell cycle progression and control. These “core” cell cycle regulators serve diverse post-mitotic functions that span various developmental stages of a neuron, including neuronal migration, axonal elongation, axon pruning, dendrite morphogenesis, and synaptic maturation and plasticity. In this review, we detail the non-proliferative post-mitotic roles that these cell cycle proteins have recently been reported to play, the significance of their expression in neurons, mechanistic insight when available, and future prospects.

### Keywords

cell cycle; neuronal migration; degradation; dendritic spines; axon pruning; synaptic scaling

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Brain development is no simple undertaking, and neither is the cell cycle. That these two processes intersect is obvious, as neural progenitors undergo extensive proliferation during brain development to generate a “master” progenitor pool from which all neurons arise. Less intuitive, however, is the physiological neuronal expression of proteins playing fundamental roles during the cell cycle. While a seemingly wasteful investment, these proteins evidently possess essential functions detached from their cell cycle ties.

An increasingly clear trend is that eukaryotic cells have evolved functionally distinct roles for many proteins. This strategy is likely economical, considering that genetic coding capacity is finite and that many processes need to be coordinated within such limitations in different cell types. Emerging evidence reveals that this holds true for a handful of core cell cycle regulators, which facilitate the differentiation and maturation of neurons. However, these “new” functions are not always an “exploitation” of their cell cycle roles, but often involve domains distinct from those required for their proliferative functions.

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The cell cycle is a highly complex and extensive process requiring the coordination of multiple events and machinery. A simple view holds that once a neural progenitor differentiates into a neuron, the post-mitotic cell has severed all ties with the cell cycle. In this scenario, the expression of cell cycle proteins can be detrimental. Indeed, this is true in the case of a dying neuron, whereby the neuron attempts to undergo cell cycle activity, or cell cycle re-entry, by inducing cell cycle proteins. This type of regulation will not be covered in this review, as it has been extensively discussed and reviewed elsewhere (Greene et al., 2004; Herrup and Yang, 2007; Kruman, 2004; Neve and McPhie, 2006; Raina et al., 2004).

This review focuses on the handful of “core” cell cycle proteins that not only regulate fundamental cell cycle processes, but also exert cell cycle-independent functions in neurons, and is organized around the neurodevelopmental stages of their actions: neuronal migration, axonal growth, axon pruning, dendrite morphogenesis, dendritic spine formation, and synaptic plasticity (Figure 1). Within these developmental contexts, the basic cell cycle functions of the implicated proteins are described, followed by a discussion of their neuronal functions, and when available, mechanistic insight.

## The cell cycle

The alternative cell cycle-independent functions that core cell cycle regulators play in neurons are best appreciated by first considering the context in which they carry out their well-established roles – the cell cycle (Figure 1). A fundamental requirement for any proliferating cell, whether a fibroblast or a neural progenitor, is to replicate its DNA and divide. Comprised of 4 distinct stages, the unidirectional progression of the eukaryotic cell cycle is ensured by checkpoints and the oscillating expression of cell cycle proteins.

During the first gap phase of the cell cycle, or G1, cells assimilate environmental signals that allow them to progress through the “restriction point,” a point after which a cell is committed to divide. G1 progression is promoted by cyclin-dependent kinase (CDK) 4/cyclin D and CDK6/cyclin D, but also kept in check by CDK inhibitors (CKIs) of the *Inhibitor of kinase 4/Alternative Reading Frame* (INK4a) and Cip/Kip families, which inhibit CDK-cyclin complexes. A major obstacle for progressing into S-phase involves the derepression of E2F transcription factors. Kept inactive by the Retinoblastoma (Rb) tumor suppressor protein, E2F proteins are activated as Rb becomes hyper-phosphorylated by CDK4, CDK6, and CDK2/cyclin E over the course of G1 progression (Nevins, 2001). Derepressed E2F proteins can then proceed to induce downstream target genes required for subsequent cell cycle progression, including cyclins (D, E, and A), DNA polymerase, CDC6, mini-chromosome maintenance (MCM) proteins, and origin recognition complex (ORC) proteins. Another important feature of G1 is the preparation of DNA replication origins, or DNA licensing, through the recruitment of pre-replication complexes (Figure 1).

Once cells have passed the restriction point, they commit to DNA replication and cell division. DNA replication and centrosome duplication occur in S-phase, which is driven by CDK2/cyclin E and CDK2/cyclin A. DNA replication initiates on multiple origins located throughout the genome bound by pre-replication complexes formed in G1. DNA polymerase, the enzyme responsible for DNA replication, is recruited to origins by the concerted actions of protein kinases, including Cdc7, CDK2/cyclin E, and CDK2/cyclin A (Woo and Poon, 2003). Once replication origins fire, re-replication of DNA is prevented via phosphorylation of replication complex components by S-phase CDKs. Given the importance of faithful genome replication, cells have evolved quality control mechanisms, or checkpoints, to ensure sufficient time to repair any damage DNA accrued during or following replication (i.e., intra-S-phase and G2/M checkpoints, respectively). The importance of these quality control mechanisms are

underscored by the various diseases, including cancer, that result from the absence of key checkpoint proteins.

Once the entire genome is duplicated, cells enter a second gap phase, or G<sub>2</sub>, during which cells verify the fidelity of DNA replication prior to mitosis. If DNA is somehow damaged during replication, cells arrest at the G<sub>2</sub>/M checkpoint and repair the damage. Once DNA replication fidelity is confirmed in G<sub>2</sub>, cells undergo mitosis and equally partition genomic material into daughter cells. Mitosis is comprised of 4 distinct phases: prophase, metaphase, anaphase, and telophase, followed by cytokinesis, or cell division. Cells achieve many feats within the span of about an hour during mitosis, including nuclear envelope breakdown, chromosome condensation, chromosome alignment at the metaphase plate, sister chromatid separation, reformation of the nuclear envelope, and cell division. Proper execution of mitotic events are monitored and controlled by the mitotic spindle checkpoint, a mechanism to ensure that kinetochores, chromosomal structures to which spindle fibers attach, are properly attached to the mitotic spindle.

These basic cell cycle concepts and mechanisms, most of which derive from studies in transformed cells, hold true in neural progenitors of the developing brain. However, the context of the developing brain provides an extra layer of spatiotemporal control on the cell cycle not observed in a culture dish. For instance, the G<sub>1</sub> phase of the cell cycle plays a crucial role in determining when a neural progenitor will undergo cell cycle exit and neuronal differentiation, or neurogenesis. During the period of neurogenesis, which peaks at around E14 in mice, G<sub>1</sub> length in progenitors increases, and this correlates with increased cell cycle exit (Takahashi et al., 1995). Supporting this, artificially lengthening the G<sub>1</sub> phase of the cell cycle can induce neurogenesis (Calegari and Huttner, 2003). Spatially, distinct cell cycle phases in neural progenitors are carried out with positional discrimination in the proliferative ventricular zone in a process called interkinetic nuclear migration (Figure 2). This spatiotemporal coordination of neural progenitor cell cycle dynamics in the developing brain ensures that a precise number of neurons and specific neuronal subtypes are generated.

## Neuronal differentiation and migration

Following a period of proliferation, neural progenitors differentiate into post-mitotic neurons. Neurons extend processes, or neurites, from the cell body through cytoskeletal rearrangements that culminate in axonal or dendritic differentiation. This process is integrated into the program of neuronal migration, whereby newly born neurons migrate radially toward the cortical plate or tangentially from the ganglionic eminence (Ayala et al., 2007). The final product of this integrated process is a multilayered cerebral cortex, in which later born neurons make up more superficial layers and early born neurons make up deep layers in an “inside-out” pattern. Processes that form and differentiate over the course of neurogenesis and neuronal migration subsequently find their targets and form characteristic connections with neurons throughout the brain. This requires the assimilation of extracellular cues and the precise coordination of many cell intrinsic events, such as cytoskeletal remodeling (actin and microtubules), establishment of polarity, protein ubiquitination, and gene transcription. Interestingly, the core cell cycle regulators p27<sup>Kip1</sup>, p57<sup>Kip2</sup>, Rb, and E2F are important mediators of neuronal migration (Figures 1 and 3).

## Inhibitors as promoters: Cell cycle inhibitors and neuronal migration

Coordinating the cell cycle requires both positive and negative regulators. Among the negative regulators are 2 families of tumor suppressors, the Cip/Kip and INK4 CKIs (Besson et al., 2008; Canepa et al., 2007). While the INK4 proteins specifically target CDK4/cyclinD and CDK6/cyclinD during G<sub>1</sub>, the Cip/Kip proteins (p21<sup>Cip1</sup>, p27<sup>Kip1</sup>, and p57<sup>Kip2</sup>) are more versatile and inhibit a broader spectrum of CDK-cyclin complexes. The mechanism of CDK

inhibition by p27<sup>Kip1</sup> involves tight association with CDK-cyclin complexes, effectively preventing them from binding to ATP ((Russo et al., 1996)). The importance of p27<sup>Kip1</sup> during the cell cycle is underscored by phenotype of p27<sup>Kip1</sup> knockout mice, which are significantly larger than wild type littermates and exhibit increased organ size (including the brain), increased cell proliferation in various organs, and increased tumorigenesis (Fero et al., 1998; Fero et al., 1996).

In addition to their roles as CKIs, Cip/Kip proteins regulate cell motility and migration by facilitating actin cytoskeleton rearrangement in many cell types (Goukassian et al., 2001; Wang et al., 2008; Wu et al., 2006). Importantly, this cell cycle-independent role involves the non-nuclear pool of CKIs, underscoring the spatial discrimination between their roles in proliferation and cell motility (Denicourt and Dowdy, 2004; McAllister et al., 2003). Cip/Kip proteins promote cell motility and migration by inhibiting the Rho signaling pathway. Interestingly, mechanisms of Rho pathway inhibition are distinct between Cip/Kip proteins: p27<sup>Kip1</sup> binds to RhoA, preventing it from binding guanine-nucleotide exchange factors (GEFs)(Besson et al., 2004); p57<sup>Kip2</sup> inhibits a downstream effector of the Rho signaling pathway, LIM domain-containing protein kinase (LIMK), by sequestering it in the nucleus (Yokoo et al., 2003); and p21<sup>Cip1</sup> binds to and inhibits ROCK1, a Rho kinase (Lee and Helfman, 2004; Tanaka et al., 2002).

Among the 2 families of CKIs, only the Cip/Kip proteins have been actively examined in terms of their post-mitotic functions. While p21<sup>Cip1</sup> and p57<sup>Kip2</sup> are expressed in neurons of the cortical plate, p27<sup>Kip1</sup> more broadly regulates brain development and is expressed in all layers of the developing cerebral cortex (Nguyen et al., 2006).

p27<sup>Kip1</sup> is receiving attention as an important mediator of neuronal migration. Given that an increase in G1 length is associated with neuronal differentiation, a straightforward hypothesis would be that p27<sup>Kip1</sup> impacts neuronal differentiation by inhibiting G1 CDKs. Altering cell cycle duration would impact the rate of neurogenesis, and ultimately, cell positioning. While inherently difficult to ascribe a cell cycle-independent function to a cell cycle protein, bypassing the cell cycle function of p27<sup>Kip1</sup> by introducing a mutation that prevents its interaction with CDK-cyclin complexes proved instrumental in identifying its cell cycle-independent function in neuronal differentiation and migration (Nguyen et al., 2006). p27<sup>Kip1</sup> loss-of-function impairs neuronal differentiation and migration, resulting in decreased neurogenesis and an accumulation of cells in the ventricular/subventricular zone of the developing cortex. Importantly, defects observed in p27<sup>Kip1</sup> knockout brains are not due to an aberrant cell cycle, since reintroducing a mutant p27<sup>Kip1</sup> that cannot bind CDK-cyclin complexes completely rescued these defects. Its role in neuronal migration, at least in part, derives from stabilization of the pro-neural transcription factor neurogenin-2 (Ngn2). Supporting this, Ngn2 overexpression rescues the neuronal migration defect elicited by p27<sup>Kip1</sup> loss-of-function (Nguyen et al., 2006).

Functionally, p27<sup>Kip1</sup> intersects with a major neuronal migration signaling pathway controlled by CDK5, an atypical cyclin-dependent kinase whose activity is restricted to neurons (Dhavan and Tsai, 2001). This finding linked a conserved role for p27<sup>Kip1</sup> in cell migration with a neuron specific kinase activity. p27<sup>Kip1</sup> stabilization by CDK5 phosphorylation on serine 10 and threonine 187 results in cofilin phosphorylation and decreased F-actin levels at neuronal processes (Kawauchi et al., 2006). This paradigm shift revealed that Cdk5-mediated neuronal migration involves rearrangements of not only microtubules, but also the actin cytoskeleton. The association between p27<sup>Kip1</sup> and CDK5 also highlights a unique situation where p27<sup>Kip1</sup> fails to inhibit CDK activity. This results from the inability of p27<sup>Kip1</sup> to recognize the CDK5 activator protein p35 as a cyclin. Indeed, while CDK5/cyclinD complexes are inhibited by p27<sup>Kip1</sup>, CDK5/p35 complexes are resistant (Lee et al., 1996). One intriguing

possibility is that neurons evolved a CDK complex resistant to CKI inhibition in order to co-opt the conserved function of p27<sup>Kip1</sup> in cell motility and adapt it to neuronal migration.

Regulation of the cytoskeleton is a function shared by p57<sup>Kip2</sup>, a CKI also expressed in migrating neurons that regulates the RhoA-cofilin pathway (Yokoo et al., 2003). This provides for potential functional crosstalk or overlap between CKIs during neuronal migration. The fact that both p27<sup>Kip1</sup> and p57<sup>Kip2</sup> are induced during neuronal differentiation and that p57<sup>Kip2</sup> knockdown resulted in a neuronal migration defect, but not a neurogenesis defect, further underscores the overlapping but distinct roles that CKIs play in neuronal differentiation and migration (Itoh et al., 2007).

### Rb and E2F3

Although introducing every transcriptional regulator reported to function in both proliferative and post-mitotic contexts is beyond the scope of this review, both Rb and E2F transcription factors deserve special mention as core cell cycle regulators playing unexpected roles in neuronal migration.

Originally discovered to be mutated in the eye, it is now well established that Rb is a central mediator of cell cycle progression (Giacinti and Giordano, 2006; Khidr and Chen, 2006). Rb's major function in the cell cycle is to sequester and inhibit E2F transcription factors in order to control the timing of DNA replication (Nevins, 2001). When cyclin D/E-dependent CDK activities become more pronounced as cells approach G1/S, Rb is gradually phosphorylated on multiple proline-directed serines and threonines, ultimately resulting in a hyperphosphorylated form of Rb that is incompatible with E2F binding. E2F transcriptional targets are also subjected to an additional layer of repression involving Rb-mediated histone deacetylase recruitment and chromatin remodeling (Brehm et al., 1998; Ferreira et al., 1998; Luo et al., 1998; Magnaghi-Jaulin et al., 1998). Upon release from hyperphosphorylated Rb, E2F proteins gain access to promoters of genes required for DNA replication and promote downstream cell cycle progression (Sun et al., 2007). Deregulation of Rb has consequences in the developing brain – ectopic DNA replication and mitoses in the retina and central nervous system. These defects are also observed in telencephalon-specific Rb knockouts (Ferguson et al., 2002).

E2F proteins are the most studied targets of Rb. Comprised of 8 genes (E2F1-E2F8), E2F gene products heterodimerize with dimerization partner proteins (DP1-DP4) to positively or negatively regulate transcription. Many genes required for cell cycle progression are E2F transcriptional targets, including DNA polymerases, MCM proteins, ORC proteins, cdc6, and cyclins. Although E2F proteins can somewhat compensate for loss of other isoforms, studies in model organisms clearly define their essential role in cell proliferation. *Drosophila* encodes one activator E2F, one repressor E2F, and one DP. Activator E2F mutants are inviable and exhibit severely reduced DNA synthesis and cell proliferation (Brook et al., 1996; Neufeld et al., 1998). In mammals, combined genetic ablation of E2F1, E2F2, and E2F3 prevents cell proliferation (Wu et al., 2001). Importantly, ectopic mitoses and DNA synthesis observed in the retina and central nervous system of Rb knockouts are lost in combined Rb, E2F1, E2F3, and E2F3 knockouts (Saavedra et al., 2002).

It is hardly surprising that Rb would be involved in neurogenesis considering its essential function during the cell cycle. Given that cell cycle length prominently figures into neuronal differentiation, alterations in cell cycle dynamics influences neurogenesis. More surprising, however, is the implication of Rb in neuronal migration. Rb loss-of-function elicits radial and tangential migration defects in cortical neurons and interneurons, respectively (Ferguson et al., 2005). Remarkably, the inability of interneurons to undergo efficient tangential migration is highly dependent on a compromised functional interaction with E2F3 (McClellan et al.,



2007). As mentioned above, Rb conditional knockouts exhibit defective tangential interneuron migration. This defect is rescued in Rb-E2F3 double knockouts but not in Rb-E2F1 knockouts, suggesting a specific role for E2F3 in carrying out Rb-mediated migration. Similar to E2F1 and E2F2, E2F3 is an “activating” E2F made up of 2 isoforms generated by alternate promoters (Adams et al., 2000; Leone et al., 2000). Among genes in ganglionic eminence cells regulated by Rb were those implicated in neuronal migration, including neogenin, Sema3d, VLDLR, ApoE, CCK, TWIST1, and Twist neighbor (McClellan et al., 2007) (Figure 3). However, a rigorous demonstration of whether these genes are direct E2F3 transcriptional targets is still lacking.

In addition to a specific role in tangential migration, E2F3/Rb also plays a cell cycle-independent role during retinal cholinergic neuron differentiation. A retinal cell undergoes a characteristic series of differentiation steps, originating as a retinal precursor cell, transitioning into a post-mitotic retinal transition cell, and terminally differentiating into a specific subtype of retinal neuron. The Rb-E2F3 (more specifically, the E2F3a isoform) pathway is essential for cholinergic starburst amacrine cell (SAC) differentiation (Chen et al., 2007). Although transcriptional targets mediating this effect have not been identified, this finding provides another specific context for the Rb-E2F3 pathway in neurons that cannot be compensated for by other E2F family members.

## Axonal growth, Dendrite morphogenesis, and Axon pruning

Neurons begin to extend processes soon after differentiation. With time, neurons become polarized, extending a single axon while remaining neurites become dendrites. The extension of an axon to its cognate target involves the assimilation of extrinsic signals, including repulsive and attractive cues, and integration with cytoskeleton remodeling mechanisms. Furthermore, these processes are projected excessively and compete for connectivity with target neurons. The ensuing competition ultimately culminates in a win-or-lose battle, and results in the refinement of axons through “pruning” or “synaptic elimination.” This collective process is thought to underlie the specificity of neuronal connections in the nervous system. Recent studies have revealed that the degradation machinery active during the cell cycle impacts axonal growth and dendrite morphogenesis. To make things more interesting, a complex that keeps sister chromatids together in proliferating cells is required for axon pruning (Figures 1 and 4).

### Cdh1 keeps the axon in check; Cdc20 promotes dendrite morphogenesis

The oscillatory expression of cell cycle proteins, including cyclins, CKIs, and various kinases, is a fundamental feature of cell cycle progression. In addition to CKIs, the proteasomal machinery and its associated accessory and regulatory proteins ensure temporal precision and unidirectional progression of the cell cycle. Key degradation events during the cell cycle are carried out by 2 ubiquitin ligase complexes: the SCF family of ubiquitin ligases and the anaphase promoting complex/cyclosome (APC/C) (Nakayama and Nakayama, 2006; Vodermaier, 2004). Proteins ubiquitinated by these complexes are targeted for degradation by the 26S proteasome.

The APC/C consists of at least 11 different subunits and degrades proteins during mitosis and G1. Its activation and substrate specificity is controlled by association with the activating subunits Cdc20 and Cdh1 (Peters, 2006). These activators recognize specific degradation motifs, KEN- (KENxxxN) and D-boxes (RxLxxxxN), on substrates and promote mitotic progression, sister chromatid separation, and mitotic exit (Pfleger and Kirschner, 2000; Pfleger et al., 2001). Given that substrate recognition is based on consensus sequences that are not post-translationally modified (in contrast to SCF E3 ligases which target phosphorylated substrates), APC/C activity is kept under tight control to prevent premature substrate

degradation during cell cycle progression. This is regulated in part by phosphorylation; phosphorylation by CDC2/cyclin B and Plk1 activates APC/C, whereas phosphorylation by PKA is inhibitory (Golan et al., 2002; Kotani et al., 1998; Kraft et al., 2003). APC/C is also controlled by association with proteins that activate (CBP and p300) and inhibit (Emi1, Bub3, BubR1, and Mad2) its activity (Fang et al., 1998; Sudakin et al., 2001; Turnell et al., 2005).

APC/C<sup>Cdc20</sup> is active during early mitosis and targets 2 major substrates, Securin and cyclin B1 (Pines, 2006). Anaphase onset and sister chromatid separation requires Securin degradation by APC/C<sup>Cdc20</sup>. Once Securin is degraded, the activated protease Separase cleaves cohesin, a protein essential for sister chromatid adhesion. APC/C<sup>Cdc20</sup> also promotes mitotic exit by targeting cyclin B1 for degradation. Initially kept from interacting with APC/C by CDC2/cyclin B phosphorylation, Cdh1 associates with APC/C following cyclin B1 degradation and targets substrates important for mitotic exit and G1 progression (Kramer et al., 2000; Visintin et al., 1998; Zachariae et al., 1998).

In addition to degrading Cdc20, APC/C<sup>Cdh1</sup> targets various substrates for degradation from mid-mitosis to G1. Mitotic exit requires degradation of the APC/C<sup>Cdh1</sup> substrates Plk1 and Aurora A (Lindon and Pines, 2004; Littlepage and Ruderman, 2002). In G1, APC/C<sup>Cdh1</sup> keeps CDK activity low by degrading cyclin A and the F-box protein Skp2 (Bashir et al., 2004; Geley et al., 2001; Sorensen et al., 2001; Wei et al., 2004). Consequently, Skp2 degradation results in increased p27<sup>Kip1</sup> expression, which in turn inhibits G1 CDK activity. APC/C<sup>Cdh1</sup>, and perhaps APC/C<sup>Cdc20</sup>, also regulates pre-replication complex formation by degrading Geminin, the Cdt1 inhibitor, during mitosis and G1 (McGarry and Kirschner, 1998). After replication origins fire in S-phase, Emi1 inactivates APC/C<sup>Cdh1</sup>, Geminin is stabilized, and re-replication is prevented.

Aside from these well established cell cycle roles, recent findings have implicated APC/C<sup>Cdh1</sup> and APC/C<sup>Cdc20</sup> in axonal growth and dendrite morphogenesis, respectively. A hint that Cdh1 might have cell cycle-independent functions in neurons came from a pioneering study reporting its expression and inclusion into an active post-mitotic APC/C complex. Cdh1 is highly expressed in tissue containing differentiated cells (Gieffers et al., 1999) and recent studies have furthered this observation by providing important insight into neuronal functions. Konishi et al. initially demonstrated that Cdh1 resides in an active APC/C complex in neuronal nuclei and that Cdh1 knockdown in cultured cerebellar granule neurons resulted in increased axonal growth without affecting dendrites (Konishi et al., 2004). This phenotype was recapitulated in the rat cerebellum, providing a relevant *in vivo* context where Cdh1 cell autonomously controls axon extension and patterning. These findings suggested the possibility that regulation of protein abundance in the nucleus may be a major pathway regulating axonal growth.

Evidence for such a possibility came from follow up studies demonstrating that Cdh1 mediates the degradation of at least two nuclear proteins, the inhibitor of DNA binding 2 (Id2) protein and the transcriptional co-repressor SnoN. Id2 is degraded by APC/C<sup>Cdh1</sup> through a D-box, and its stabilization increases axonal growth (Lasorella et al., 2006). A similar phenotype results from APC/C<sup>Cdh1</sup>-mediated SnoN degradation; namely, SnoN loss-of-function impairs and its stabilization increases axonal growth (Stegmuller et al., 2006). *In vivo*, SnoN is required for the development of IGL granule neuron parallel fibers, underscoring the importance of this pathway during brain development. Furthermore, this APC/C<sup>Cdh1</sup>-SnoN axis is under the control of an upstream Smad2-dependent TGF $\beta$  signaling pathway mediated by Smad2 (Stegmuller et al., 2008). Consistent with Smad2's involvement in axonal growth, its knockdown increases axonal growth, further establishing the TGF $\beta$  signaling pathway as a cell intrinsic repressor of axonal growth. These findings are likely relevant to nerve regeneration after neuronal injury. The inability to regenerate has been linked to the inhibitory influence of

myelin through Nogo receptors (Chen et al., 2000; GrandPre et al., 2000). Importantly, Cdh1 knockdown or Id2 stabilization overrides the repression by myelin, highlighting this pathway as a promising therapeutic target (Konishi et al., 2004; Lasorella et al., 2006).

The striking similarities between the Id2 and SnoN knockdown phenotypes prompts the question of whether these two pathways intersect or are distinct pathways regulating axonal growth. While no direct evidence that links these two pathways has been reported, evidence from other biological processes suggests that TGF $\beta$  signaling influences Id2 expression. TGF $\beta$  signaling impacts Id2 expression differently depending on context. During lymphocyte development, TGF $\beta$  signaling induces Id2 expression (Sugai et al., 2003), while Id2 expression is repressed in response to the TGF $\beta$  signaling-induced cytostatic response (Kang et al., 2003; Siegel et al., 2003). The impact that TGF $\beta$  signaling has on Id2 expression and SnoN-mediated axonal growth suggests the potential involvement of an Id2-SnoN pathway, a possibility that can be addressed through epistatic experiments.

In contrast to the nuclear functions of APC/C<sup>Cdh1</sup> in axon growth, APC/C<sup>Cdc20</sup> functions at the centrosome to regulate dendrite morphogenesis. In a recent study, Cdc20 was found to be highly expressed in post-mitotic neurons. Intriguingly, Cdc20 loss-of-function impairs dendrite growth and branching in cerebellar granule neurons *in vitro* and *in vivo* (Kim et al., 2009), an effect independent of Cdh1. Conversely, Cdc20 knockdown has no effect on axonal growth. One of the remarkable findings of this study is that Cdc20 needs to be specifically localized to the centrosome to impact dendrite morphogenesis. Mechanistically, Cdc20 interacts with HDAC6 at the centrosome and promotes dendrite growth through Id1 degradation. In addition to delineating a novel function for APC/C<sup>Cdc20</sup> in dendrite morphogenesis, this study prompts the search for other APC/C<sup>Cdc20</sup> substrates that may function in other contexts, such as synaptic plasticity (see “APC/C functions at the synapse” section).

The functions of APC/C in post-mitotic neurons are only beginning to unravel. As a ubiquitin ligase, APC/C likely targets multiple neuron-specific substrates. Furthermore, such targeting can occur in both nuclear and non-nuclear compartments. Future studies are likely to reveal that APC/C factors into many facets of neuronal function, ranging from neuronal differentiation to synaptic plasticity.

### Cohesin: pruning with a ring

After DNA replication, a mitotic cell segregates its two copies of chromosomes into two daughter cells. A major effort during mitosis is focused on chromosomal segregation, which requires cohesion of sister chromatids, a process carried out by a multisubunit complex called cohesin (Gruber et al., 2003; McNairn and Gerton, 2008; Uhlmann, 2004). Four core members (SCC1/Rad21, SCC3, SMC1, and SMC3) interact, forming a 35-nm ring that holds sister chromatids together through a topological mechanism that involves the trapping of DNA inside the ring (Gruber et al., 2006). Cohesin activity is also dependent on interactions with regulatory factors, including PDS5, SCC2, SCC4, and ECO1 (Nasmyth and Haering, 2005).

Cohesin is bound along chromosomes throughout interphase. In mitosis, sister chromatid separation during anaphase is mediated by Separase, which cleaves the Rad21 subunit of the cohesin complex and promotes chromatid release from the ring. This pool of cohesin represents a minor fraction of total cohesin, however, and most cohesin complexes dissociate from chromosomes during prophase through a Separase-independent mechanism. These intact cohesin complexes can then reassociate with chromosomes in G1 (reviewed in (Liu and Krantz, 2008). Dissociation of cohesin from chromosomes during prophase is under the control of many kinases that reduce its affinity for chromatin, including CDC2/cyclin B (Losada et al., 2000), Plk1 (Hauf et al., 2005), and Aurora B (Losada et al., 2002). The essential role of cohesin in sister chromatid cohesion is evidenced by the increased distance between sister chromatids



observed with cohesin loss-of-function (Losada et al., 2005; Toyoda and Yanagida, 2006). While its essential role for proper mitotic progression is conserved from yeast to humans, recent studies have reported unexpected cell cycle-independent roles for cohesin in neurons.

The importance of the cohesin complex in human development is underscored by the cohesin-associated disorder Cornelia de Lange syndrome (CdLS). Multiple components of the cohesin complex, as well as its regulatory factors, are causal genes for this disorder. Interestingly, evidence supporting a role for cohesin outside chromatid cohesion comes from CdLS patients (Dorsett, 2007; Musio et al., 2006). Nervous system-related anomalies seen in CdLS patients include microcephaly and mental retardation. These anomalies were not attributed to cell proliferation defects, implying that cohesin may have cell cycle-independent functions in the brain (Strachan, 2005). Many of the abnormalities seen in CdLS patients can be recapitulated in mice lacking PDS5B, a cohesin accessory protein highly expressed in post-mitotic neurons of the brain. Anomalies associated with PDS5B knockout mice were widespread, including facial dysmorphisms, cleft palate, skeletal patterning defects, and heart defects. Furthermore, ptosis and gastrointestinal disorders experienced by CdLS patients may derive from defects in peripheral and enteric nervous system development observed in these mice, including abnormal projections of the superior cervical ganglia (SCG) to target organs and abnormal innervation and ganglion formation in the neonatal bowels (Zhang et al., 2007).

Two recent studies examining axonal development of *Drosophila* mushroom body neurons support the notion that cohesin functions in axon pruning and dendritic targeting. The clever strategies used to ascribe a cell cycle-independent function by timing the loss of cohesin function revealed cohesin's role in neurons. In one study, a mosaic screening strategy in *Drosophila* identified two cohesin subunits essential for axon pruning, SMC1 and SA (Schuldiner et al., 2008). The axon pruning defect was cell cycle-independent given that reintroducing SMC1 into affected neurons rescued axon pruning. SMC1 mutants also exhibit aberrant dendritic targeting of olfactory projection neurons that was also rescued by post-mitotic complementation with SMC1. A different approach involving temporally restricted cleavage of Rad21 also demonstrated the requirement for cohesin in axon pruning (Pauli et al., 2008). Both studies identified the loss of ecdysone receptor (EcR-B1) expression as a contributing factor to the pruning defect, which was reversed by EcR-B1 overexpression. This finding was further strengthened by the discovery that cohesin bound to the EcR genomic locus (Misulovin et al., 2008).

How does cohesin carry out its neuronal functions? Some studies support the involvement of regulated gene expression, as cohesin is strategically localized to control transcription; cohesin regulates EcR-B1 expression and associates with chromatin during G1 (Gullerova and Proudfoot, 2008; Pauli et al., 2008; Schuldiner et al., 2008). Further support for this possibility comes from a reported interaction between cohesin and CCCTC-binding factor (CTCF) with downstream effects on transcriptional insulation (Parelho et al., 2008; Rubio et al., 2008; Stedman et al., 2008; Wendt et al., 2008).

A number of issues remain unresolved. It is currently unclear whether cohesin is required for axonal pruning and dendritic targeting in mammalian neurons. If it is, transcriptional targets mediating this effect need to be identified. Another intriguing question is whether cohesin-mediated axon pruning converges with previously reported axon pruning pathways, such as the plexin-semaphorin pathway (Bagri et al., 2003; Liu et al., 2005), the TGF $\beta$  signaling pathway (Zheng et al., 2003), the ubiquitin-proteasome system (Watts et al., 2003), and cytoskeletal remodeling (Gallo, 2006) pathways. To this end, it will be interesting to see whether cohesin's transcriptional targets bridge cohesin-mediated axon pruning with these pathways. Given that synaptic connections are modified throughout the life of an organism, another possibility is that cohesin contributes to morphological changes in a manner similar to

the plexin-semaphorin pathway. For instance, in addition to playing a role in axon guidance, semaphorins are involved in the formation of *Drosophila* giant fiber synapses (Godenschwege et al., 2002).

## The post-synaptic compartment and synaptic plasticity

Once the fundamental architecture and necessary connections have been established in a mature neuron, further morphological changes that strengthen or weaken synapses occur in response to neuronal activity. While local post-translational modifications are sufficient to elicit short term changes in synaptic strength, long term changes require active transcription and protein synthesis. In the postsynaptic compartment, dendritic spines harbor the majority of glutamatergic synapses. Dendritic spine size and morphology change in response to neuronal activity and involve local reorganization of the actin cytoskeleton. As would be expected for a dynamically fluctuating system, biological processes such as synaptic scaling exist to positively or negatively regulate synapses and prevent runaway plasticity. Core cell cycle regulators also function in these contexts to regulate dendritic morphology, post-synaptic local translation, and homeostatic plasticity (Figures 1 and 4).

## APC/C functions at the synapse

In addition to exerting its influence from nuclei and centrosomes, APC/C can also act locally in post- and pre-synaptic compartments to regulate synaptic strength in mature neurons. In *Drosophila*, the neuromuscular junction (NMJ) provides an excellent model system to study the interaction between pre- and post-synaptic compartments. Core components of the APC/C complex localize to the NMJ and APC/C mutants exhibited increased synaptic size due to a doubling of boutons per synapse. This was associated with increased levels of liprin- $\alpha$ , a protein important for presynaptic organization and synaptic size in model systems ranging from *C.elegans* to mice (van Roessel et al., 2004). On the postsynaptic side, APC/C regulates *Drosophila* end plate potentials in muscles by controlling the number of glutamate receptors. Unlike the requirement for APC/C activity in the nucleus or centrosome, these distinct APC/C functions are carried out by its localized activity in pre- and post-synaptic terminals (Stegmuller et al., 2006). Further evidence supporting a role for APC/C in synaptic development comes from a study performed in *C. elegans*. An increase in GLR-1 receptor abundance was observed with temperature-sensitive APC/C mutants, restrictive temperature-based mutants that bypass the cell cycle defect associated with compromising APC/C function (Juo and Kaplan, 2004). As GLR-1 does not contain D- or KEN-boxes, the most likely scenario involves deregulation of the receptor recycling machinery. The importance of controlling GLR-1 abundance by APC/C is underscored by the behavioral consequences resulting from APC/C loss-of-function; specifically, a defect in spontaneous *C. elegans* locomotion due to increased synaptic strength (Juo and Kaplan, 2004).

Synaptic defects and behavioral consequences are also observed in Cdh1 heterozygous knockout mice. Although basal synaptic transmission in the CA1 region, paired-pulse facilitation, and early-phase long-term potentiation (LTP) were unchanged compared to wild type mice, long-phase LTP was defective in heterozygous mice. Heterozygous mice also exhibited impaired fear conditioning, a hippocampus-dependent process (Li et al., 2008). Although the evidence is still tentative at best, Cdc20 may also regulate synaptic function. The control of its expression by Egr1 potentially implicates it in late-phase LTP. Egr1 is induced after induction of long-term potentiation (LTP) in the hippocampus, and Egr1 knockout mice have impaired late-phase hippocampal LTP. Importantly, Egr1 knockouts express more Cdc20 in the brain and Cdc20 expression decreases in response to NMDA receptor stimulation (Conway et al., 2007). Future work should clarify whether defects in Egr1 knockout mice are attributable to the enhanced degradation of Cdc20 substrates, and whether Cdc20 targets substrates specifically at the centrosome in this context.

### Synaptic licensing: ORCs at the post-synaptic compartment

While conceivable that a nuclear complex like cohesin controls axon pruning through a transcriptional mechanism, it is conceptually difficult to rationalize ORC function in neurons, where its localization is mainly non-nuclear. ORC is comprised of multiple proteins (ORCs 1-6) and its function to restrict genome replication to one round during the cell cycle is highly conserved in eukaryotes. All ORC subunits are required for DNA replication and their loading onto replication origins during G1 serves as a platform for the sequential recruitment of pre-replication complex components, including Cdc6, Cdt1, and the MCM complex (Bell and Dutta, 2002). Prevention of DNA re-replication is achieved through ORC inactivation by phosphorylation or ubiquitination, and the mechanism involved varies depending on the particular organism or cell type examined (reviewed in (DePamphilis, 2005)). For instance, limiting DNA replication to S-phase requires the degradation of human ORC1 by SCF<sup>Skp2</sup> in S-phase (Mendez et al., 2002). Despite this mechanism, some ORC1 persists past S-phase and this pool is inhibited by CDK1/cyclin A through phosphorylation. Phosphorylation by CDK1 prevents ORC1 from associating with chromatin during mitosis, and represents another means to prevent DNA re-replication (Li et al., 2004).

ORC proteins can also function outside DNA replication to regulate heterochromatin formation, DNA-replication checkpoints, mitotic chromosome assembly, sister chromatid cohesion, cytokinesis, and ribosome biogenesis (Sasaki and Gilbert, 2007). Paralleling its participation in transcriptional repression in yeast, mammalian ORC interacts with HP1, a mediator of heterochromatin formation (Pak et al., 1997). ORC proteins are also involved in chromosome condensation. ORC2 associates with kinetochores during mitosis and promotes chromosome condensation by recruiting CDK1 to chromatin (Cuvier et al., 2006). A striking consequence of ORC2 knockdown is abnormal chromosome condensation (Prasanth et al., 2004). Interestingly, these various cell cycle-independent functions are carried out by domains distinct from those required during DNA replication.

ORC's role in the nervous system was not initially surprising, given that its function was unknown at the time of its discovery. In a *Drosophila* P-element based screen for memory-related genes, genes required for flies to learn to avoid noxious odors identified the autosomal gene *latheo* (Boynton and Tully, 1992). Consistent with its Greek translation of "to cause a person not to know," *latheo* mutants fail to remember being presented with noxious stimuli coupled to an electric shock in a classical Pavlovian learning paradigm. Only after nearly a decade had past was the surprising discovery made that *latheo* encoded an ORC subunit. Two different experimental approaches provided alternative explanations as to why *latheo* mutant flies fail to learn. In a study by Pinto et al., *latheo* mutants exhibited severely reduced proliferation in the CNS that resulted in defective brain architecture. Importantly, they identified *latheo* as an ORC subunit (Pinto et al., 1999), providing a potential neurodevelopmental basis for the learning defect. Rohrbough et al. provided more unexpected insights by detailing a role for *latheo* in neurons at the *Drosophila* neuromuscular junction (NMJ), a region where some genes involved in learning and memory have conserved roles in synaptic plasticity (Rohrbough et al., 1999). At the NMJ, *latheo* localizes to synaptic boutons where it regulates synaptic transmission. Basal synaptic transmission amplitude is increased and various forms of activity-dependent synaptic plasticity are impaired in *latheo* mutants (Rohrbough et al., 1999). While direct verification of these findings in higher mammals is still lacking, mouse neurons express multiple ORC proteins (ORC2-6) localized to the post-synaptic compartment (Huang et al., 2005). Knockdown of ORC proteins in cultured hippocampal neurons profoundly decreases dendritic spine density and dendritic branching. Unlike loss-of-function of many postsynaptic proteins, ORC disruption resulted in a very selective defect, as PSD-95 accumulation and spine morphology remained normal, hinting at a functional divergence between initiation of spine formation and maturation. These findings

make it clear that two apparently distinct functions of *latheo*/ORC can directly (at the post-synaptic compartment) and indirectly (reduced progenitor proliferation) contribute to learning, memory, and dendritic complexity.

The non-nuclear localization of ORC proteins in mammalian and *Drosophila* neurons is intriguing considering that ORC's proliferative role is carried out in the nucleus. The finding that ORC1 is not expressed in neurons indicates a cell cycle-independent function of the ORC at the post-synapse, given that all ORC proteins are required for DNA replication (Huang et al., 2005). While the lack of solid evidence makes it premature to ascribe a mechanism underlying ORC function in neurons, its role during proliferation leaves room for speculation. ORC6 can associate with the actin cytoskeleton during mitosis (Prasanth et al., 2002), suggesting that ORC proteins might regulate cytoskeletal changes at synapses. Interestingly, the association with actin is mediated by a domain independent of its replicative function (Chesnokov et al., 2003). Combined with the finding that ORC subunits regulate dendritic morphology and dendritic spines, this would establish a more direct role at the synapse consistent with the synaptic transmission defects observed in *Drosophila latheo* mutants.

### **Aurora A: A centrosomal kinase directs translation at the synapse**

Among the essential kinases that function in mitosis are Aurora kinases, evolutionarily conserved serine-threonine kinases that maintain genomic stability and are required for mitotic progression. Although they share conserved regions, each member (Aurora A, B, and C) contributes distinctly to cell cycle progression. Aurora A is essential for mitotic entry, centrosome maturation during late G2 and prophase, centrosome separation during bipolar spindle assembly, and mitotic spindle organization (Giet et al., 2005). Its role in mitotic entry is to phosphorylate Plk1 and activate CDK1/cyclin B through phosphorylation of Cdc25B at centrosomes (Dutertre et al., 2004). During mitotic progression, Aurora A loss-of-function prevents centrosomal separation prior to mitotic spindle formation and results in monopolar spindles (Glover et al., 1995; Liu and Ruderman, 2006).

Aurora B also plays multiple roles during mitosis, including promotion of chromosome condensation for sister chromatid separation, removal of cohesin from sister chromatids through Shugoshin phosphorylation, facilitation of mitotic spindle assembly through MCAK and Stathmin phosphorylation, destabilization of chromosomal attachment to kinetochores to ensure proper segregation of sister chromatids, and execution of anaphase and cytokinesis through phosphorylation of proteins essential for cytokinesis (reviewed in (Vader and Lens, 2008)). In contrast to Aurora A and B, a role for Aurora C in cell cycle progression is debatable. While its transcripts are detectable outside reproductive tissue, Aurora C protein is specifically expressed in the testes and required for male fertility in mice (Kimmins et al., 2007; Tang et al., 2006).

While Aurora B function seems to be limited to proliferating cells, Aurora A is expressed in the hippocampus and regulates synaptic plasticity. In *Xenopus* oocytes, Aurora A phosphorylates the cytoplasmic polyadenylation element binding factor (CPEB) during oocyte maturation (Sarkissian et al., 2004). This phosphorylation event, in turn, primes the recruitment of a multiprotein polyadenylation complex required for downstream polyadenylation of cytoplasmic polyadenylation element (CPE)-containing mRNAs. Interestingly, hippocampal neurons co-opt this machinery and downstream signaling pathways to carry out stimulus-induced polyadenylation at the post-synaptic compartment.

Building on work that originally implicated CPEB-1 in synaptic activity-induced polyadenylation and translation of CaMKII mRNA (Wu et al., 1998), Huang et al. successfully bridged polyadenylation mechanisms from two seemingly unrelated processes, *Xenopus* oocyte maturation and synaptic plasticity, by implicating a common Aurora A intermediate

(Huang et al., 2002). Consistent with a function in synaptic plasticity, Aurora A is enriched at the post-synaptic compartment of hippocampal neurons. In a synaptosome-based system containing active Aurora A, stimulation of glutamate receptors by NMDA treatment resulted in CPEB-1 phosphorylation on an Aurora A specific site. This signaling cascade was responsible for NMDA-dependent polyadenylation and subsequent local translation of  $\alpha$ CaMKII mRNA. While the intermediate steps coupling NMDA receptor activation to Aurora A activation remains elusive, these findings nonetheless provided important insight into NMDA receptor-mediated local protein synthesis in dendrites with potential implications in hippocampal LTP. Consistent with this idea, CPEB-1 knockout mice display defects in certain types of LTP and LTD (Alarcon et al., 2004), and in *Aplysia*, a neuronal isoform of CPEB promotes synaptic protein synthesis in an activity-dependent manner to maintain long term facilitation (Si et al., 2003). More recently, Zearfoss et al. implicate local translation of c-jun mRNA and the downstream induction of growth hormone (GH) expression in the CPEB→synaptic plasticity circuit (Zearfoss et al., 2008). Although they lack the Aurora A phosphorylation sites present in CPEB-1, other CPEB family members are also important for synaptic plasticity (Theis et al., 2003).

It is tempting to speculate that regulated Aurora A expression may allow for negative feedback control during NMDA receptor-mediated plasticity events that require post-synaptic local translation. Such a regulatory circuit, if one exists, may implicate APC/C<sup>Cdh1</sup>. Supporting such a possibility, both Aurora A and APC/C are located post-synaptically and Aurora A is a well established APC/C<sup>Cdh1</sup> substrate (Littlepage and Ruderman, 2002; Taguchi et al., 2002).

### Spiking dendrites with Plk2

Polo-like kinases (PLKs) are evolutionarily conserved serine-threonine kinases that contain conserved polo-boxes and play important roles during cell cycle progression and genotoxic stress (Barr et al., 2004). Comprised of four members (Plk1-4), substrate specificity is often dictated by PLK localization and recognition of phosphorylated substrates via polo-box domains (PBDs). The most extensively studied member of this family, Plk1, was originally identified in a yeast screen for mutants defective in cell division (Hartwell et al., 1973). Since that pioneering study, Plk1 has been shown to regulate almost every key step in G2 and mitosis, including mitotic entry, centrosome maturation, cohesin release from sister chromatids, chromosomal segregation, and cytokinesis (Petronczki et al., 2008). Consistent with its mitotic function, Plk1 is localized to centrosomes and kinetochores during mitosis and its expression increases during late S phase and persists into mitosis. Plk1 contributes to these various processes through phosphorylation of multiple targets, including Wee1 and Myt1 kinases (mitotic entry), Cdc25 (mitotic entry), Nlp1 (centrosomal maturation),  $\gamma$ -tubulins (centrosomal maturation), cohesin (sister chromatid separation), APC/C subunits (chromosomal segregation), NudC (cytokinesis), and MKlp2 (cytokinesis) (reviewed in (van de Weerd and Medema, 2006)).

Functions of the remaining PLKs are more elusive. Plk2 and Plk3 expression peaks a few hours after serum stimulation of quiescent NIH3T3 fibroblast cells; in effect, they function as immediate early genes (Winkles and Alberts, 2005). Consistent with their rapid induction in response to stimuli, they also function as stress-response genes. Plk2 is broadly distributed in various tissues and plays a role in centrosome duplication during S phase, and prepares centrosomes for further Plk1-mediated maturation in late G2 (Warnke et al., 2004). In contrast to Plk1, Plk3 plays an inhibitory role in cell growth (Conn et al., 2000). In fact, Plk1 is often overexpressed in cancers, whereas Plk3 levels are downregulated in many cancers (Winkles and Alberts, 2005). Plk4, the most recently identified PLK family member, is essential for cell cycle progression. Similar to Plk1, Plk4 functions during mitosis, where it regulates centriole biogenesis and late mitotic progression (Hudson et al., 2001; Ko et al., 2005; Rodrigues-



Martins et al., 2007). Plk4 knockout embryos exhibit increased anaphase arrest, and heterozygous MEFs display reduced cell proliferation (Ko et al., 2005).

Expression of Plk2 and Plk3 in the nervous system was first reported about 15 years ago (Donohue et al., 1995; Simmons et al., 1992). However, insight into their functions remained elusive until one study revealed that their messages increased in response to neuronal activity induced by high frequency stimulation and drug-induced seizures (Kauselmann et al., 1999). Both proteins bound to Cib, a calcium- and integrin-binding protein, via their PBDs. More recently, a number of important studies have solidified a role for Plk2 in shaping dendritic protrusions harboring excitatory synapses, or dendritic spines.

As might be surmised from its expression in the hippocampus, Plk2 is important for synaptic plasticity and remodeling. Pak et al. first revealed that morphological changes occurring in response to synaptic activity are likely attributed to Plk2-induced ubiquitin-mediated degradation of the spine-associated Rap guanosine triphosphatase activating protein (SPAR) (Pak and Sheng, 2003). SPAR and Plk2 associate *in vivo* and this interaction promotes SPAR proteolysis. Consistent with this, Plk2 overexpression resulted in reduced spine formation and a loss of PSD-95, while expression of kinase-dead Plk2 promoted spine formation.

The Plk2-SPAR degradation pathway is essential for homeostatic plasticity, a mechanism by which neurons normalize synaptic activity to within an optimal range in the face of chronic excitation or depression (Turrigiano, 2008). Seeburg et al. add a new molecular perspective to this process by introducing a novel Cdk5-Plk2-SPAR axis in the fine-tuning of synaptic strength (Seeburg et al., 2008). Increasing or decreasing Plk2 activity results in increased or dampened synaptic strength, respectively. Furthermore, degradation-resistant SPAR disrupts synaptic homeostasis. The molecular mechanisms involved in this “synaptic scaling” parallel a well established mechanism for degrading PLK substrates during the cell cycle. The implication of CDK5, however, provides a neuron-specific context to this phenomenon. SPAR needs to be “primed” by CDK5 phosphorylation of Serine 1328 in order for it to associate with Plk2. Once phosphorylated, Plk2-bound SPAR is targeted for degradation (Seeburg et al., 2008). The importance of CDK5 in this process is underscored by the impaired synaptic scaling that results from CDK5 inhibition. Further mechanistic insight into SPAR degradation was provided by an informative array of biochemical experiments (Ang et al., 2008). SPAR harbors a canonical  $\beta$ -TrCP phosphodegron, which when phosphorylated, recruits SCF $^{\beta}$ -TrCP and promotes SPAR degradation. These collective mechanistic findings are paralleled by data in cycling cells, whereby Plk1-mediated  $\beta$ -TrCP degron phosphorylation facilitates SCF $^{\beta}$ -TrCP recruitment to a number of its substrates, including Wee1 (Watanabe et al., 2005; Watanabe et al., 2004), Emi1 (Margottin-Goguet et al., 2003; Moshe et al., 2004), Claspin (Mamely et al., 2006; Peschiaroli et al., 2006), and Bora (Seki et al., 2008). These findings confirm that the sequential CDK/PLK $\rightarrow$ substrate $\rightarrow$ degradation pathway is conserved in post-mitotic neurons.

## Concluding Remarks and Future Outlook

The recent years have seen a marked increase in reports of novel functions for core cell cycle regulators in neurons. This list is likely to expand given that the number of these proteins that are expressed in neurons without characterized neuronal functions remains extensive. For instance, while the Cip/Kip proteins have been investigated in depth for their role in neuronal migration, the INK4 proteins have not. Interestingly, p19<sup>INK4d</sup> is expressed in post-mitotic neurons and its expression regulated by excitotoxic stimuli (Zindy et al., 1997). Revisiting the functions of such proteins will provide us with a better understanding of the extent to which they exert physiological cell cycle-independent neuronal functions.

A key difficulty in defining a neuron-specific function to a core cell cycle regulator is the lingering possibility that an underlying cell cycle defect may indirectly cause the resultant neuronal phenotype. This is especially true for developmental studies, where altering cell cycle dynamics can indirectly result in the generation of different neuronal subtypes and alter brain architecture. Many studies have bypassed such limitations through RNAi-mediated knockdown of proteins in primary neuronal cultures or *ex vivo* transfection of brain slices by gene gun. To address a cell cycle-independent role and relevance *in vivo*, many studies have spatiotemporally controlled the deletion of a gene using inducible conditional Cre-lox genetic systems. Harnessing expression at the spatiotemporal level offers wide flexibility in terms of when (to address both cell cycle role and neuronal role) and where (specific neuronal subtypes) the protein of interest is disrupted.

Among the cell cycle proteins likely to have further neuronal functions are the ubiquitin ligases, of which APC/C is the pioneer ligase. For one, many of the proteins described in this review are direct targets of APC/C during cell cycle progression, suggesting the possibility that the neuronal processes regulated by these proteins may in turn be influenced by APC/C. It also begs the question of whether other APC/C cell cycle substrates are expressed in neurons and whether their degradation is similarly regulated by APC/C. Aside from APC/C, a number of cell cycle ubiquitin ligases, especially of the SCF family, likely play important roles in neurons. For instance, the F-box protein  $\beta$ -TrCP degrades SPAR, with downstream morphological changes in dendritic spines as mentioned previously. SKR-1, an ortholog of the SKP-1, is implicated in synapse elimination in *C. elegans* (Ding et al., 2007). Ultimately, bioinformatic approaches will likely prove useful in the identification of further substrates based on known target consensus sequences, such as phosphodegrons and D-boxes.

The advent of novel strategies that allow spatiotemporal loss- and gain-of-function of a gene provides a unique opportunity to revisit the functions of core cell cycle regulators in neurons, especially for those proteins whose chronic loss-of-function is lethal. While the first step in the process is to ascribe a phenotype associated with compromising gene function, current research is, for the most part, not at the level of ascribing specific functions to these proteins at a mechanistic level. Given that only a handful of core cell cycle regulators have been shown to play physiological cell cycle-independent roles in neurons thus far, further identification of such proteins may reveal underlying concepts and/or patterns that provide a clear link between their seemingly distinct cell cycle and neuronal functions. Another issue to consider is whether these proteins exert other functions in different neuronal contexts. An example of this is the requirement for APC/C not only in early neuronal maturation events, but also for pre- and post-synaptic events in mature neurons. Along these lines, existing studies hint that a network of functional interactions may exist between core cell cycle regulators in neurons as exists during the cell cycle. Supporting such a possibility, some proteins described in this review are direct substrates of APC/C during the cell cycle and a recent study describes a functional interaction between the ORC and cohesin in cycling cells (Shimada and Gasser, 2007). Future work should provide interesting insights into how core cell cycle regulators evolved to meet the demands of different cellular contexts and promote rigorous pursuits of mechanisms surrounding their post-mitotic functions.

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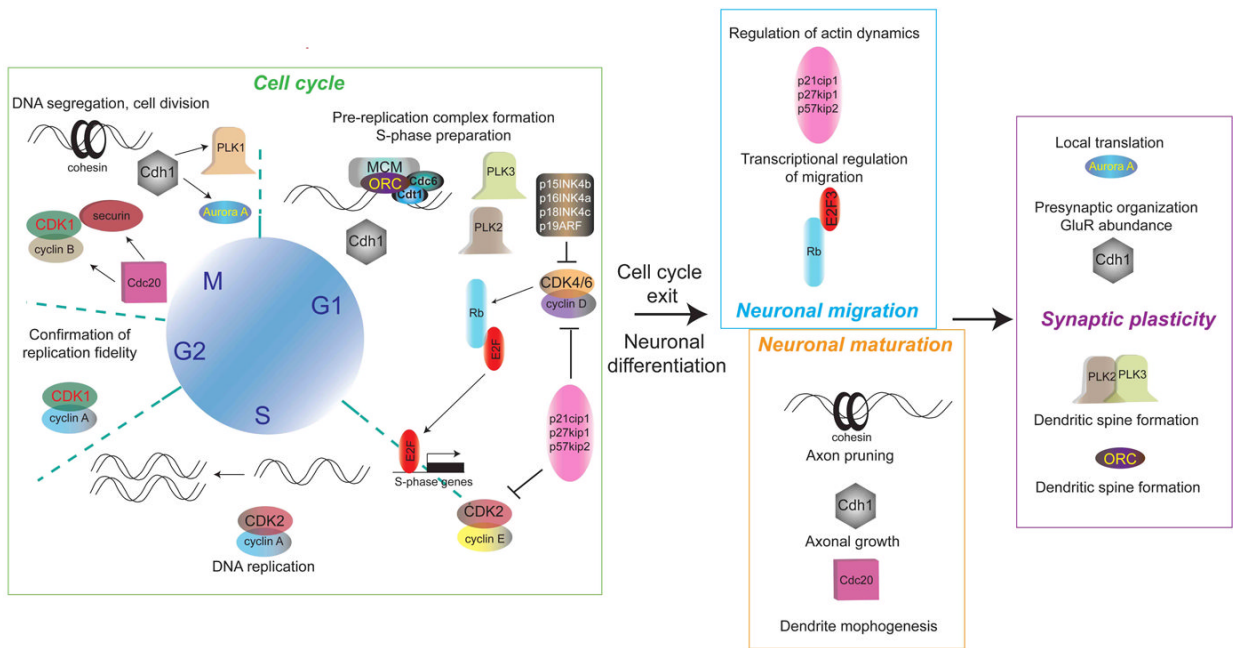
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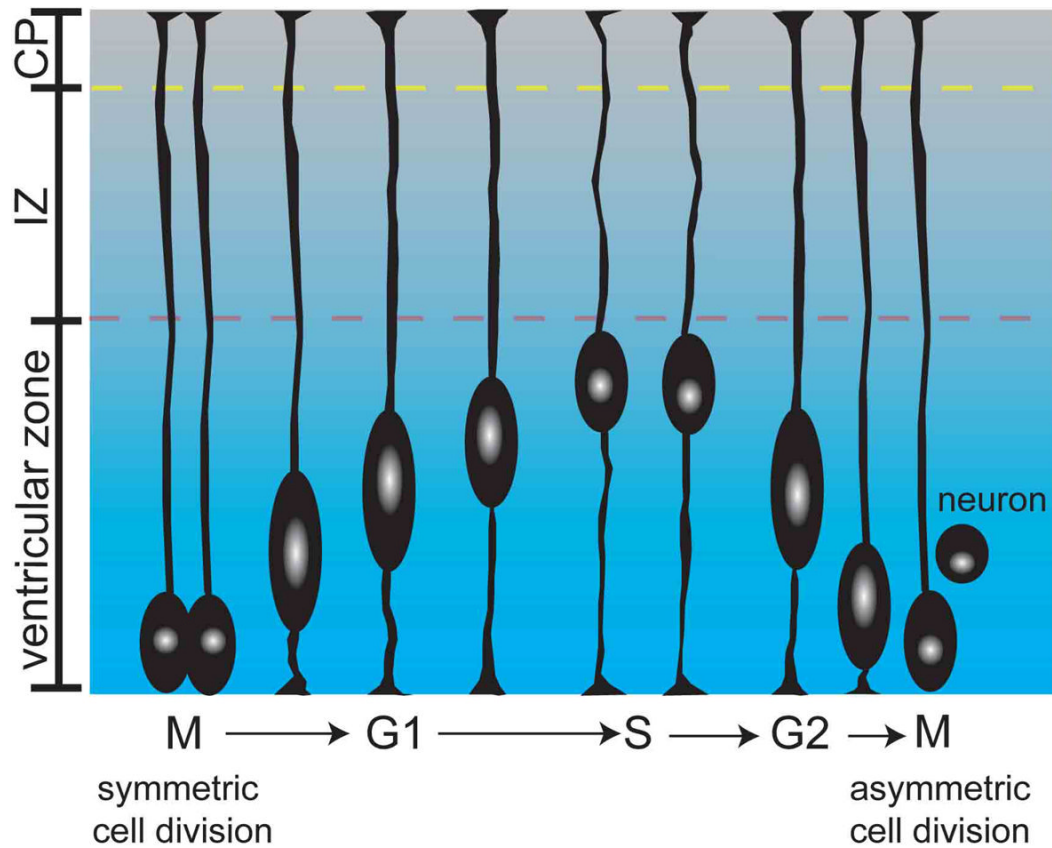
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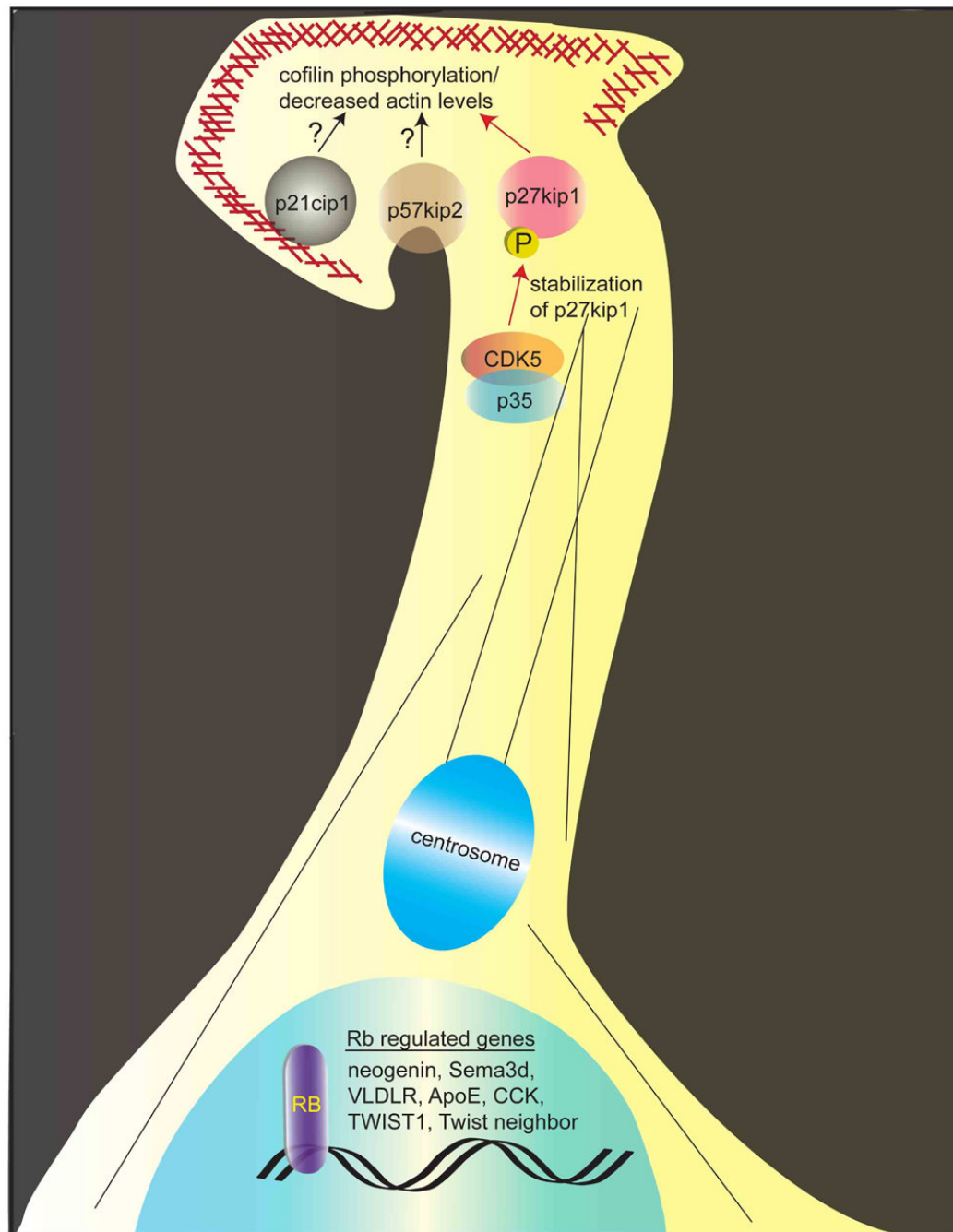
**Figure 1. Developmental flow: from the cell cycle to synaptic plasticity**

The mammalian cell cycle consists of 4 distinct phases: G1, S, G2, and mitosis. Cell cycle progression is ensured by oscillatory CDK and cyclin expression. Within this framework, the core cell cycle regulators discussed in this review regulate multiple aspects of cell cycle progression that span pre-replicative complex formation, protein degradation, transcription, sister chromatid adhesion, and cell division. After proliferating neural progenitors exit the cell cycle and differentiate into neurons, they undergo a maturation process involving axonal (Cdh1, cohesin) and dendritic differentiation (Cdc20, cohesin) while migrating (CKIs, Rb, E2F3) to their final destinations. Once proper synaptic connections have been made, mature neurons exhibit synaptic plasticity in response to neuronal activity (Cdh1 (Cdc20?), ORC, Aurora A, PLK2/3).



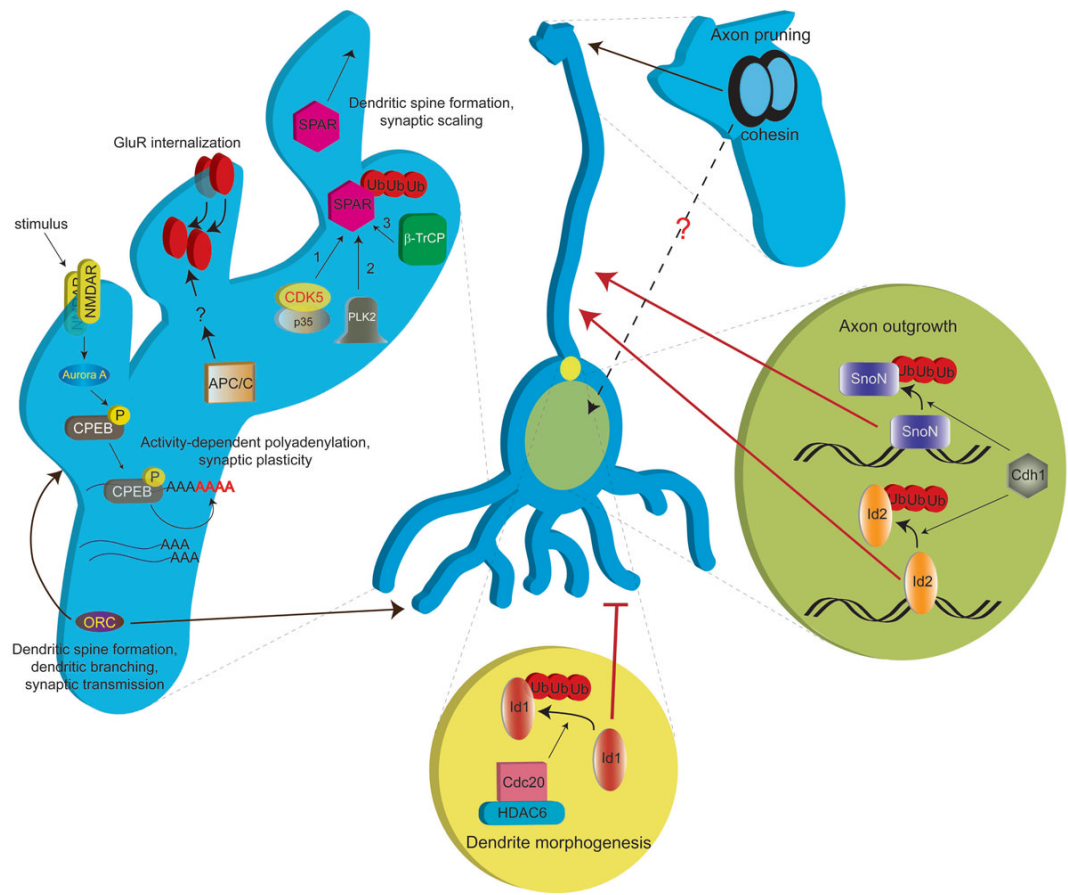
**Figure 2. Interkinetic nuclear migration**

Proliferating progenitor cells of the developing cerebral cortex undergo a characteristic pattern of nuclear migration during cell cycle progression. Nuclei of neural progenitors are positioned near the ventricular surface during G1 and gradually migrate basally as cells approach S-phase. As cells progress through S-phase towards G2, nuclei migrate apically toward the ventricular surface, where progenitors eventually undergo mitosis.



### Figure 3. Cell cycle inhibitors and the Rb protein in neuronal migration

The Cip/Kip family of CKIs regulate the actin cytoskeleton during neuronal migration by inhibiting the Rho signaling pathway. While p27<sup>Kip1</sup> and p57<sup>Kip2</sup> are important for neuronal migration, a role for p21<sup>Cip1</sup> has not been reported. Cdk5 regulates the stability of p27<sup>Kip1</sup>, which in turn promotes cofilin phosphorylation. Whether p57<sup>Kip2</sup> and p21<sup>Cip1</sup> promote neuronal migration through a similar mechanism remains unclear. In the nucleus, Rb, and possibly E2F3, is essential for the expression of genes implicated in neuronal migration.



**Figure 4. Core cell cycle regulators are implicated in diverse neuronal processes**

Core cell cycle regulators function in the nuclear, centrosomal, pre-synaptic, and post-synaptic compartments in neurons to control neurite outgrowth, axon elongation and pruning, dendrite morphogenesis, dendritic spine formation and branching, synaptic scaling, activity-dependent local translation, synaptic transmission, synaptic plasticity, and receptor internalization. See text for details.