Regulation of APC/C-Cdh1 and Its Function in Neuronal Survival

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Abstract Neurons are post-mitotic cells that undergo an active downregulation of cell cycle-related proteins to survive. The activity of the anaphase-promoting complex/cyclosome (APC/C), an E3 ubiquitin ligase that regulates cell cycle progression in proliferating cells, plays a relevant role in post-mitotic neurons. Recent advances in the study of the regulation of APC/C have documented that the APC/C-activating cofactor, Cdh1, is essential for the function(s) of APC/C in neuronal survival. Here, we review the normal regulation of APC/C activity in proliferating cells and neurons. We conclude that in neurons the APC/C-Cdh1 complex actively downregulates the stability of the cell cycle protein cyclin B1 and the glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3. Keeping these proteins destabilized is critical both for preventing the aberrant reentry of post-mitotic neurons into the cell cycle and for maintaining their reduced antioxidant status. Further understanding of the pathophysiological regulation of these proteins by APC/C-Cdh1 in neurons will be important for the search for novel therapeutic targets against neurodegeneration.

Keywords APC/C • Cdh1 • Cell cycle regulation • Neuronal survival • Neurodegeneration

Abbreviations

APC/C Anaphase-promoting complex/cyclosome
CNS Central nervous system
Cdk Cyclin-dependent kinase
D box Destruction box
PFKFB3 6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3
NMDA N-methyl-D-aspartate
PPP Pentose-phosphate pathway
RING Really interesting new gene
SCF Skp1-Cul1-F-box-protein
TGFβ Transforming growth factor β
TPR Tetratricopeptide
UPS Ubiquitin proteasome system
ZBR Zinc-binding region

Introduction

The cell cycle is an essential process for the development, differentiation, and proliferation of eukaryotic cells. Classically, the cell cycle is divided into four phases, namely, G1, S, G2, and M. Proper progression from one phase to the other is monitored by checkpoints that sense possible defects during DNA synthesis and chromosome segregation [1]. Progression through the cell cycle is controlled by the appropriate and timely activation of cell cycle proteins. This control is executed by the ubiquitin proteasome system (UPS). The UPS consists of sets of enzymes that target substrates to proteasomal destruction by covalently attaching a poly-ubiquitin chain in an enzymatic cascade [2]. First, ubiquitin is covalently linked to the E1 ubiquitin-activating enzyme in an energy (ATP)-dependent manner. Ubiquitin is then transferred to the E2 ubiquitin-conjugating enzyme. Finally, the E3 ubiquitin ligase recruits both the E2 ubiquitin-conjugating enzyme and substrate, thus
facilitating the transfer of ubiquitin to the lysine residues of the substrate. Polyubiquitinated substrates are then recognized by the proteasome, which leads them to degradation [2].

The specificity of the UPS is conferred by a large and varied collection of E3 ubiquitin ligases. The cullin-really interesting new gene (RING)-finger-type E3s constitute one of the largest classes of E3s and are essential for the maintenance of genomic integrity and cellular homeostasis [3]. Two major cullin-RING-E3 ubiquitin ligases, the SKP1-CUL1-F-box-protein (SCF) complex and the anaphase-promoting complex, also called the cyclosome (APC/C), are responsible for targeting cell cycle proteins for degradation. Whereas SCF ubiquitylates substrates from late G1 to early M phase, the APC/C is active from the onset of mitosis to the end of the G1 phase of the cell cycle [4, 5]. Differentiated cells, such as neurons, remain resting in the G0 phase due to an active downregulation of cell cycle-related proteins. However, recent evidence has indicated that neurons retain the ability to reactivate the cell cycle in response to central nervous system (CNS) insults. Thus, neurons attempt to reenter the cell cycle under pathological circumstances, including both acute injury and chronic neurodegenerative disorders [6–8]. For instance, in vivo evidence has revealed S phase entry in ischemic neurons [9] and aberrant expression of mitotic cyclin B1 in degenerating neurons in Alzheimer’s disease [10]. Thus, dysregulation of the cell cycle machinery might be a pathway common to several neurodegenerative disorders and other CNS diseases [11]. It has recently been reported that APC/C activity, which regulates cell cycle progression in proliferating cells [12–14], is also essential for neuronal survival [15, 16], linking proliferation to neurodegeneration. This review summarizes recent findings describing the functions of APC/C in neuronal cell death.

The APC/C Complex

The APC/C is a multi-subunit cullin-RING E3 ubiquitin ligase assembled from 13 different core subunits that regulate progression from metaphase to anaphase and exit from mitosis [12–14, 17]. Among these subunits, the best-characterized ones are the cullin and RING proteins Apc2 and Apc11, which are responsible for catalytic activity, the tetratricopeptide (TPR) repeat subunit Apc3 (or Cdc27), which interacts with co-activators, and the Apc10, also known as Doc1 [17, 18]. The RING-finger protein Apc11 interacts directly with the Ub-conjugated E2 enzyme, while the cullin domain of Apc2 interacts with the RING-finger domain of Apc11, acting as a scaffold to connect Apc11 to the enzyme [19].

Regulation of the APC/C in the Cell Cycle

The activity of the APC/C is tightly regulated along the cell cycle. This is exerted through a combination of co-activator subunits, reversible phosphorylation, and inhibitory proteins and complexes [12–14]. To be active, the APC/C requires the binding of either one of two WD40-domain co-activator proteins, Cdc20 or Cdh1, which also participate in substrate recognition [20–22]. The activators interact dynamically with the TPR domains in Apc3 and may either facilitate recruitment of substrates through their WD40 domains or enhance the specific activity of the APC/C [23]. The TPR subunit Apc3 also interacts with the Apc10 subunit [24]. Apc10 contains a β-barrel structure, known as the Doc domain that is involved in substrate binding and recognition [25, 26].

Activation of the APC/C by Cdc20 or Cdh1 is regulated tightly and oppositely by phosphorylation events. In early mitosis, cyclin–cyclin-dependent kinase (Cdk) complexes phosphorylate some APC/C subunits, hence promoting the binding of Cdc20 to the complex [27]. APC/C-Cdc20 thus initiates a sequence of degradation of mitotic cyclins that results in decreased Cdk activity, leading to the initiation of anaphase. In contrast, the phosphorylation of Cdh1 by Cdks during S phase, G2, and mitosis inhibits its binding to the APC/C [28, 29]. During exit from mitosis, the inactivation of Cdks and subsequent activation of phosphatases [30] allows Cdh1 dephosphorylation, leading to the activation of the APC/C-Cdh1 complex. In turn, APC/C-Cdh1 ubiquitylates Cdc20, thus preventing the simultaneous activation of both APC/C co-activators. APC/C-Cdh1 also targets A/B types of mitotic cyclins for destruction, completing the inactivation of Cdk1. In particular, cyclin B1 is degraded in two phases, sequentially regulated by APC/C-Cdc20 and APC/C-Cdh1 [31, 32]. Subsequently, during early mitosis, Cdc20 activates APC/C, whereas in late mitosis APC/C-Cdh1 activation controls mitotic exit and G1 maintenance, thus regulating the onset of DNA replication [12–14].

Substrate Recognition by APC/C-Cdh1

APC/C-Cdc20 and APC/C-Cdh1 have different substrate specificities, which allow the orchestration of cell cycle protein degradation in the correct order. Selection of the APC/C targets is controlled by the recognition of short degron motifs, predominantly the destruction (D) box (RxxLxx(N)) and the KEN box (KENxxxN) [17]. The D box was first described to be necessary and sufficient for the
The subcellular localization of Cdh1 provides an important element of spatial regulation of APC/C-Cdh1 activity. For example, Cyclin-Cdks blocks its own interaction and binding to APC/C-Cdh1, leading to Skp2 accumulation at the end of G1 phase [56, 57]. On the other hand, Cdc14B-dependent dephosphorylation of Cdh1 promotes Skp2 degradation at the M/G1 transition [58].

In addition to inhibitory phosphorylation by Cdk5, Cdh1 is also inhibited by Emi1, which acts as a pseudosubstrate that inactivates APC/C-Cdh1 at G2 and G1/S transition. Finally, Cdh1 mediates its own degradation by stimulating APC/C activity, which depends upon two D boxes.

Phosphorylation of Cdh1 and APC/C Activity

The activity of APC/C-Cdh1 increases in late anaphase and is maintained elevated through the G1 phase of the cell cycle, and it is tightly regulated through the reversible phosphorylation of Cdh1 and its substrates, inhibitor proteins, and Cdh1 degradation (Fig. 1). The phosphorylation of Cdh1 by Cdk1 and Cdk2, which starts from G1/S transition to anaphase, blocks its own interaction and binding to APC/C [28]. Recently, it has been described that Cdk5, a member of the CNS predominant Cdk family that is essential for synaptic plasticity [45] and neurotoxicity [46, 47], phosphorylates (and inactivates) Cdh1 [16].

It is known that Cdh1 dephosphorylation depends not only on Cdk inactivation but also on phosphatase activation [30]. In budding yeast, the main Cdh1 phosphatase, Cdc14, mediates the activation of both Cdh1 and the Cdk1 inhibitor protein Sic1, leading to the completion of Cdk1 inactivation [48, 49]. However, although three homologues of yeast Cdc14 (CDC14A, CDC14B, and CDC14C) have been identified in vertebrates, their relevance remains unclear, given the lack of a clear effect on mitotic exit [50–53]. By contrast, mitotic exit in animal cells is independent of Cdc14 and, instead, relies on phosphatases of the PP1 and PP2A families [30]. In this context, numerous studies suggest functions of vertebrate Cdc14 that are unrelated to mitotic exit, including roles in the DNA damage checkpoint [54], DNA repair [53], and centrosome duplication and function [51, 55]. In particular, in response to genotoxic stress in G2, Cdc14B translocates from the nucleolus to the nucleoplasm, where this phosphatase dephosphorylates Cdh1, hence promoting APC/C-Cdh1 activity [54].

The phosphorylation of Cdh1 substrates also contributes to the regulation of APC/C-Cdh1 activity. For example, Cdk2-mediated phosphorylation of the SCF E3 ubiquitin ligase cofactor, Skp2, disrupts its association with APC/C-Cdh1, leading to Skp2 accumulation at the end of G1 phase [56, 57]. On the other hand, Cdc14B-dependent dephosphorylation of Cdh1 promotes Skp2 degradation at the M/G1 transition [58].

In addition to inhibitory phosphorylation by Cdk5, Cdh1 is also inhibited by Emi1, which acts as a pseudosubstrate that inactivates APC/C-Cdh1 at G2 and the G1/S transition [59–61]. Emi1 contains a D box motif that mediates its own binding to APC/C-Cdh1, thus blocking the accessibility of substrates to the enzyme. Moreover, Emi1 also contains a ZBR motif that directly inhibits APC/C E3 ligase activity [62].

Fig. 1 Regulation of APC/C-Cdh1 activity. The activity of APC/C-Cdh1 is tightly regulated by reversible phosphorylation of Cdh1, inhibitor proteins, and Cdh1 degradation. The phosphorylation of Cdh1 by cyclin-Cdks blocks its own interaction and binding to APC/C-Cdh1, leading to Skp2 accumulation at the end of G1 phase. Cdh1 dephosphorylation triggers APC/C-Cdh1 activation. Dephosphorylated Cdh1 is translocated from the nuclei to the cytosol where it is recognized and targeted for degradation by the SCF complex. Cdh1 is also inhibited by Emi1, which acts as a pseudosubstrate that inactivates APC/C-Cdh1 at G2 and G1/S transition. Finally, Cdh1 mediates its own degradation by stimulating APC/C activity, which depends upon two D boxes.
APC/C-Cdh1 in G0/G1 Regulation

As mentioned above, cyclin-Cdk complexes phosphorylate Cdh1, inhibiting its binding to the APC/C complex [28, 29]; the concomitant inhibition of APC/C activity is released when cyclin-Cdk activity decreases and Cdh1 phosphorylation stops in late mitosis. This leads to APC/C-Cdh1 reactivation, which in turn maintains the cyclin B-Cdk1 inactive during late mitosis [68]. In this phase, APC/C-Cdh1 also mediates the degradation of regulators of cytokinesis and centrosome replication, such as Aurora A, Aurora B, Plk1, Anillin, and Tpx2, among other proteins [69, 70].

During G1, APC/C-Cdh1 remains active by maintaining the activity of cyclin-Cdk complexes low. In this context, active APC/C-Cdh1 targets A/B types of mitotic cyclins for proteasomal degradation [71, 72]. Moreover, APC/C-Cdh1 can also inactivate Cdk activity by promoting the degradation of the Cdk activator, Cdc25A, and the two cofactors of the SCF E3 ubiquitin-conjugating enzyme (E2) UbcH10 also provides a negative feedback mechanism that inactivates APC/C-Cdh1 during the G1/S transition.

During G1, most cells commit alternatively to DNA replication and division or to cell cycle exit and differentiation. Because of its crucial role in G1/G0 regulation and maintenance of quiescence, APC/C-Cdh1 has been proposed to be responsible for linking cell cycle exit and differentiation in certain cell types [14, 38] (Fig. 2). Bar-On et al. [77] have recently described that APC/C-Cdh1-mediated Skp2 degradation, and the subsequent p27 accumulation are essential for human embryonic stem cell differentiation.

APC/C-Cdh1 is also crucial for the coordination of cell cycle progression and the initiation of lens [78] and muscle cell [79] differentiation. APC/C-Cdh1-regulated lens differentiation is mediated by transforming growth factor (TGF)β-induced destruction of SnoN, a transcriptional repressor of the Cdk inhibitors p15 and p21 (Fig. 2). Thus, depletion of Cdh1 by RNA interference attenuates the TGFβ-mediated induction of p15 and p21 and blocks lens differentiation [78]. Furthermore, TGFβ induces Skp2 degradation mediated by the Smad cascade, which stabilizes p27 and p21 and thereby contributes to TGFβ-induced cell cycle arrest [80]. In muscle, APC/C-Cdh1 regulates two critical proteins, Skp2 and Myf5, for proteolysis during muscle differentiation [79]. On the one hand, the targeting of Skp2 by APC/C-Cdh1 for destruction results in an accumulation of p21 and p27, which are crucial for coordinating cellular division and differentiation. On the other hand, the degradation of Myf5 facilitates myogenic fusion.
APC/C-Cdh1 in Neuronal Differentiation

The activation of APC/C-Cdh1 is also required for neuronal differentiation. It has been reported that APC/C-Cdh1 mediates retinoic acid-induced neuronal differentiation from SHSY5Y neuroblastoma cells [74]. Thus, retinoic acid induces the nuclear accumulation of Cdh1 that parallels Skp2 destabilization and p27 accumulation. Furthermore, retinoic acid decreases the mRNA and protein levels of Rae1—a nuclear export factor that limits APC/C-Cdh1 activity in mitosis—hence facilitating APC/C-Cdh1-mediated Skp2 degradation, leading to cell cycle arrest and neuroblastoma differentiation [74]. The regulation of this Skp2-p27 axis by APC/C-Cdh1 has also been found to be involved in the terminal differentiation of neuronal precursors in response to nerve growth factor [81].

Finally, APC/C-Cdh1 regulates axonal growth and patterning through the degradation of two nuclear proteins, namely, the inhibitor of differentiation/DNA binding 2 (Id2) and SnoN [82, 83] (Fig. 2). In the developing nervous system, Id2 enhances cell proliferation, promotes tumor progression, and inhibits the activity of neurogenic basic helix-loop-helix transcription factors [84]. Lasorella et al. [82] demonstrated that APC/C-Cdh1 targets Id2 for degradation through a D box motif that is conserved in Id1 and Id4. Degradation of Id2 in neurons permits the accumulation of the Nogo receptor and the subsequent inhibition of axonal growth. Furthermore, Stegmuller et al. [83] found that the Cdh1-dependent inhibition of TGFβ-SnoN axis stimulates axonal growth.

Cyclin B1 Stability Regulation by APC/C-Cdh1 in Neuronal Survival

Several core subunits of APC/C and Cdh1 are highly expressed in mammalian brain post-mitotic neurons [15, 85]. In neurons, depletion of Cdh1 by RNA interference rapidly triggers apoptotic neuronal death. Thus, APC/C-Cdh1 is required to maintain low levels of cyclin B1 in order to prevent an aberrant entry into the cell cycle that will lead to neuronal apoptosis (Fig. 3). Cdh1 then regulates neuronal survival [15]. Under physiological conditions, glutamate receptor-mediated excitatory neurotransmission plays a central role in neural development, differentiation, and synaptic plasticity. However, excessive or prolonged activation of glutamate receptors induces neurotoxicity, a process that has been defined as excitotoxicity [86, 87]. Excitotoxicity mediates neuronal death in several neurological disorders, including stroke and chronic neurodegenerative diseases [87, 88]. In a previous study, the changes in cyclin B1 protein levels following an excitotoxic stimulus caused by a short (5 min) incubation of post-mitotic cortical neurons with glutamate (100 μM) or the specific glutamate receptor subtype agonist, N-methyl-D-aspartate (NMDA; 100 μM) were investigated. Under these conditions, neurons died in an NMDA receptor-dependent manner [89]. Western blot analyses of neurons revealed that both glutamate and NMDA promoted an accumulation of cyclin B1 in the neuronal nuclei that was fully prevented by silencing cyclin B1 [16]. Furthermore, cyclin B1 nuclear accumulation was responsible for a large proportion of the apoptotic death caused by glutamate and NMDA. It was also found that glutamate and NMDA triggered Cdh1 phosphorylation, sequestering Cdh1 in the cytosol and inhibiting APC-Cdh1 activity.

Using both the Cdk inhibitor roscovitine and an RNA interference strategy, it was also demonstrated that Cdh1 was phosphorylated by Cdk5, an enzyme that can be persistently activated when bound to p25 [46], the proteolytic product of p35 that has previously been shown to accumulate in the neurons of patients with Alzheimer’s disease [90]. It was found that Cdk5 small interfering RNA dose-dependently prevented the apoptotic neuronal death triggered by NMDA and glutamate. These data were the first to suggest that NMDA receptor stimulation activates Cdk5, which phosphorylates Cdh1, leading to cyclin B1 accumulation and neuronal apoptotic death [16]. It is interesting to note that Cdk5 phosphorylates the NMDA receptor NR2A subunit at Ser-1232, hence facilitating NMDA receptor synaptic transmission [91]. Thus, NMDA receptor overactivation, which occurs in prolonged release of the neurotransmitter glutamate such as that occurring in neurodegenerative diseases and stroke [88], could lead to a Cdk5-NMDA receptor activation feedback loop, contributing to the propagation of neurodegeneration.
Interestingly, cyclin B1 accumulates in degenerating brain areas in Alzheimer’s disease [10, 92] and stroke [93], which are situations known to be associated with an excitotoxic-type neuronal death [88]. Thus, these data suggest that Cdk5-mediated Cdh1 inactivation might contribute to neuronal death in neurological disorders.

**APC/C-Cdh1 in Glucose Metabolism and Oxidative Stress: Role in Neurodegeneration**

Neurons are the highest energy-consuming cells of the brain; however, the rate of glycolysis, the metabolic route responsible for the generation of most energy needs in cells, is very low in neurons, particularly in comparison with their neighboring astrocytes [94, 95]. Glucose-derived glucose-6-phosphate is the connecting metabolite between glycolysis and the pentose-phosphate pathway (PPP) [96]. The PPP is the main metabolic pathway responsible for the regeneration of NADPH(H\(^+\)), a required reducing cofactor for many oxidoreductases. Previously, it has been found that in cortical neurons the protein abundance of the glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase, isoform 3 (PFKFB3) is very low in neurons as compared with that found in astrocytes [95]. This was considered important, since PFKFB3 is a key enzyme controlling the rate of glycolysis, and hence energy generation from glucose. Furthermore, it was found that overexpressing PFKFB3 in neurons increased the rate of glycolysis, although it concurrently decreased that of the PPP [97].

Interestingly, PFKFB3 protein was found to be a substrate of APC/C-Cdh1 [97]. Accordingly, APC/C-Cdh1 activity determines the control of the rate of glucose consumption both through glycolysis and the PPP. In contrast to neurons, astrocytes express a very low Cdh1 protein abundance, and hence APC/C activity is negligible in these cells [97]. Knocking down Cdh1 in neurons inhibits APC/C-Cdh1 activity and leads PFKFB3 protein to accumulate, thus shifting glucose consumption towards glycolysis at the expense of a reduction in that of the PPP. Importantly, this causes an impairment in neurons to regenerate NADPH(H\(^+\)), hence promoting oxidative stress by promoting the oxidation of antioxidant glutathione [97].

This tight regulation of glycolysis and PPP by APC/C-Cdh1 has important consequences for neuronal survival. Thus, when the activation of the rate of glycolysis is prolonged by inhibiting APC/C-Cdh1 activity, neurons undergo apoptotic death [97]; moreover, neuronal death can be fully reversed by incubation with a plasma membrane-permeable form of glutathione [97]. Thus, glucose is preferentially utilized through the PPP to exert antioxidant-mediated neuroprotection, and APC/C-Cdh1 activity is essential to control this physiological function. Future studies will be needed to understand whether Cdh1 deficiency or the inhibition of APC/C activity exert any role in the mechanism leading to neurodegeneration.

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**References**

1. Murray AW (2004) Recycling the cell cycle: cyclins revisited. Cell 116:221–234
2. Hershko A, Ciechanover A (1998) The ubiquitin system. Annu Rev Biochem 67:425–479
3. Lipkowitz S, Weissman AM (2011) RINGs of good and evil: RING finger ubiquitin ligases at the crossroads of tumour suppression and oncogenesis. Nat Rev Cancer 11:629–643
4. Nakayama KI, Nakayama K (2006) Ubiquitin ligases: cell-cycle control and cancer. Nat Rev Cancer 6:369–381
5. Song L, Kape M (2011) Substrate-specific regulation of ubiquitination by the anaphase-promoting complex. Cell Cycle 10:52–56
6. Timms S, Menn B (2007) Cerebral ischemia, cell cycle elements and Cdk5. Biotechnol J 2:958–966
7. Shaka Y, Cooksey R, Cox JE, Wang V, McClain DA, Tantin D (2009) Oct1 loss of function induces a coordinate metabolic shift that opposes tumorigenicity. Nat Cell Biol 11:320–327
8. Hernandez-Ortega K, Quiroz-Baez R, Arias C (2011) Cell cycle reactivation in mature neurons: a link with brain plasticity, neuronal injury and neurodegenerative diseases? Neurosci Bull 27:185–196
9. Kuan CY, Schloemer AJ, Lu A, Burns KA, Weng WL, Williams MT, Strauss KI, Vorhees CV, Flavell RA, Davis RJ, Sharp FR, Rakic P (2004) Hypoxia–ischemia induces DNA synthesis without cell proliferation in dying neurons in adult rodent brain. J Neurosci 24:10763–10772
10. Vincent J, Jicha G, Rosado M, Dickson DW (1997) Aberrant expression of mitotic cdc2/cyclin B1 kinase in degenerating neurons of Alzheimer’s disease brain. J Neurosci 17:3588–3598
11. Yang Y, Herrup K (2007) Cell division in the CNS: protective response or lethal event in post-mitotic neurons? Biochim Biophys Acta 1772:457–466
12. Peters JM (2006) The anaphase promoting complex/cyclosome: a machine designed to destroy. Nat Rev Mol Cell Biol 7:644–656
13. Thornton BR, Toczyski DP (2006) Precise destruction: an emerging picture of the APC. Genes Dev 20:3069–3078
14. Eguren M, Manchado E, Malumbres M (2011) Non-mitotic functions of the anaphase-promoting complex. Semin Cell Dev Biol 22:572–578
15. Almeida A, Bolanos JP, Moreno S (2005) Cdh1/Hct1-APC is essential for the survival of postmitotic neurons. J Neurosci 25:8115–8121
16. Maestre C, Delgado-Esteban M, Gomez-Sanchez JC, Bolanos JP, Almeida A (2008) Cdk5 phosphorylates Cdh1 and modulates cyclin B1 stability in excitotoxicity. EMBO J 27:2736–2745
17. Barford D (2011) Structural insights into anaphase-promoting complex function and mechanism. Philos Trans R Soc Lond B Biol Sci 366:3605–3624
18. Matyskiewicz ME, Rodrigo-Brenni MC, Morgan DO (2009) Mechanisms of ubiquitin transfer by the anaphase-promoting complex. J Biol Sci 8:92
19. Tang Z, Li B, Bharadwaj R, Zhu H, Ozkan E, Hakala K, Deisenhofer J, Yu H (2001) APC2 Cullin protein and APC11 RING protein comprise the minimal ubiquitin ligase module of the anaphase-promoting complex. Mol Cell Biol 12:3839–3851
20. Schwaab M, Lutum AS, Seufert W (1997) Yeast Hct1 is a regulator of Cdc2 cyclin proteolysis. Cell 90:683–693
21. Sigrist SJ, Lehner CF (1997) Drosophila fuzzy-related down-regulates mitotic cyclins and is required for cell proliferation arrest and entry into intercycles. Cell 90:671–681
22. Visintin R, Prinz S, Ammon A (1997) CDC20 and CDH1: a family of substrate-specific activators of APC-dependent proteolysis. Science 278:460–463
23. Vodermaier HC, Gieffers C, Maurer-Stroh S, Eisenhaber F, Peters JM (2003) TR subunits of the anaphase-promoting complex mediate binding to the activator protein CDH1. Curr Biol 13:1459–1468
24. Wendt KS, Vodermaier HC, Jacob U, Gieffers C, Gmachl M, Peters JM, Huber R, Sondermann P (2001) Crystal structure of the APC10/DOC1 subunit of the human anaphase-promoting complex. Nat Struct Biol 8:784–788
25. Carroll CW, Enquist-Newman M, Morgan DO (2005) The APC subunit Doc1 promotes recognition of the substrate destruction box. Curr Biol 15:11–18
26. da Fonseca PC, Kong EH, Zhang Z, Schreiber A, Williams MA, Morris EP, Barford D (2011) Structures of APC/C(Cdh1) with substrates identify Cdh1 and Apc10 as the D-box co-receptor. Nature 470:274–278
27. Kraft C, Herzog F, Gieffers C, Mechtler K, Hagiing A, Pines J, Peters JM (2003) Mitotic regulation of the human anaphase-promoting complex by phosphorylation. EMBO J 22:6598–6609
28. Zachariae W, Schwaab M, Nasmyth K, Seufert W (1998) Control of cyclin ubiquitination by CDK-regulated binding of Hct1 to the anaphase promoting complex. Science 282:1721–1724
29. Kramer ER, Scheuringer N, Podtelejnikov AV, Mann M, Peters JM (2000) Mitotic regulation of the APC activator proteins CDC20 and CDH1. Mol Cell Sci 11:1555–1569
30. Wurzenberger C, Gerlich DW (2011) Phosphatases: providing safe passage through mitotic exit. Nat Rev Mol Cell Biol 12:469–482
31. Yeong FM, Lim HH, Padmeshree CG, Surana U (2000) Exit from mitosis in budding yeast: biphasic inactivation of the Cdc28-Cib2 mitotic kinase and the role of Cdc20. Mol Cell 5:501–511
32. Thornton BR, Toczyski DP (2003) Securin and B-cyclin/CDK are the only essential targets of the APC. Nat Cell Biol 5:1090–1094
33. Glotzer M, Murray AW, Kirschner MW (1991) Cyclin is degraded by the ubiquitin pathway. Nature 349:132–138
34. King RW, Deshaies RJ, Peters JM, Kirschner MW (1996) How proteolysis drives the cell cycle. Science 274:1652–1659
35. Yamano H, Gannon J, Hunt T (1996) The role of proteolysis in cell cycle progression. Schizosaccharomyces pombe. EMBO J 15:5268–5279
36. Pfleger CM, Kirschner MW (2000) The KEN box: an APC recognition signal distinct from the D box targeted by Cdh1. Genes Dev 14:655–665
37. Passmore LA, Barford D (2005) Coactivator functions in a stoichiometric complex with anaphase-promoting complex/cyclosome to mediate substrate recognition. EMBO Rep 6:873–878
38. Wasch R, Robbins JA, Cross FR (2010) The emerging role of APC/CCdh1 in controlling differentiation, genomic stability and tumor suppression. Oncogene 29:1–10
39. Littlepage LE, Ruderman JV (2002) Identification of a new APC/C recognition domain, the A box, which is required for the Cdh1-dependent destruction of the kinase Aurora-A during mitotic exit. Genes Dev 16:2274–2285
40. Reis A, Levassour M, Chang HY, Elliott DJ, Jones KT (2006) The CRY box: a second APC/Cdh1-dependent degron in mammalian cdc20. EMBO Rep 7:1040–1045
41. Castro A, Viglenor S, Bernis C, Labbe JC, Lorca T (2003) Xkid is degraded in a D-box, KEN-box, and A-box-independent pathway. Mol Cell Biol 23:4126–4138
42. Yamano H, Gannon J, Mahbubani H, Hunt T (2004) Cell cycle-regulated destruction of the destruction box of cyclin B by the APC/C in Xenopus egg extracts. Mol Cell 13:137–147
43. Carroll CW, Morgan DO (2002) The Doc1 subunit is a processivity factor for the anaphase-promoting complex. Nat Cell Biol 4:880–887
44. Passmore LA, McCormack EA, Au SW, Paul A, Willison KR, Harper JW, Barford D (2003) Doc1 mediates the activity of the anaphase-promoting complex by contributing to substrate recognition. EMBO J 22:786–796
45. Hawasli AH, Benavides DR, Nguyen C, Kansy JW, Hayashi K, Chambon P, Greengard P, Powell CM, Cooper DC, Bibb JA (2007) Cyclin-dependent kinase 5 governs learning and synaptic plasticity via control of NMDAR degradation. Nat Neurosci 10:880–886
46. Lee MS, Kwon YT, Li M, Peng J, Friedlander RM, Tsai LH (2000) Neurotoxicity induces cleavage of p35 to p25 by calpain. Nature 405:360–364
47. Hamdane M, Buee L (2007) The complex p25/Cdk5 in neurofibriillary degeneration and neuronal death: the missing link to cell cycle. Biotechnol J 2:967–977
48. Jaspersen SL, Charles JF, Morgan DO (1999) Inhibitory phosphorylation of the APC regulator Hct1 is controlled by the kinase Cdc28 and the phosphatase Cdc14. Curr Biol 9:227–236
49. Stegeimer F, Ammon A (2004) Closing mitosis: the functions of the Cdc14 phosphatase and its regulation. Annu Rev Genet 38:554–553
50. Saito RM, Perreault A, Peach B, Satterlee JS, van den Heuvel S (2003) TPR subunits of the anaphase-promoting complex comprise the minimal ubiquitin ligase module of the anaphase-promoting complex. J Mol Biol 278:460–467
51. Kaiser BK, Zimmerman ZA, Charbonneau E, Jackson PK (2002) Disruption of centrosome structure, chromosome segregation, and cytokinesis by misexpression of human Cdc14A phosphatase. Mol Biol Cell 13:2289–2300
52. Berdougo A, Nachury MV, Jackson PK, Jallepalli PV, Kirschner MW, Kaelin WG (2008) The nucleolar phosphatase Cdc14B is dispensable for chromosome segregation and mitotic exit in human cells. Cell Cycle 7:1184–1190
53. Mocciaro A, Berdougo E, Zeng K, Black E, Vagnarelli P, Earnshaw WC, Gillespie D, Jallepalli P, Schiebel E (2010) Vertebrate cells genetically deficient for Cdc14A or Cdc14B retain DNA damage checkpoint proficiency but are impaired in DNA repair. J Cell Biol 189:631–639
54. Rodier G, Freas L, Hoang D, Caudy A, Kaelin WG (2004) The SCF(Skp2-Cks1) ubiquitin ligase by the anaphase-promoting complex. Mol Cell 14:189–198
55. Green K, Kaelin WG, Hoang D, Caudy A, Kaelin WG (2004) Control of the SCF(Skp2-Cks1) ubiquitin ligase by the anaphase-promoting complex. Mol Cell 14:189–198
56. Mocciaro A, Berdougo E, Zeng K, Black E, Vagnarelli P, Earnshaw WC, Gillespie D, Jallepalli P, Schiebel E (2010) Vertebrate cells genetically deficient for Cdc14A or Cdc14B retain DNA damage checkpoint proficiency but are impaired in DNA repair. J Cell Biol 189:631–639
57. Bassermann F, Frescas D, Guardavaccaro D, Busino L, Peschiaroli B, Save A, Magrane JM, Pagnaio M (2008) The Cdc14B-Cdh1-Plk1 axis controls the G2 DNA-damage-response checkpoint. Cell 134:256–267
58. Mailand N, Lukas C, Kaiser BK, Jackson PK, Bartek J, Lukas J (2002) Deregulated human Cdc14A phosphatase disrupts centrosome separation and chromosome segregation. Nat Cell Biol 4:317–322
59. Wei W, Ayad NG, Van Y, Zhang GJ, Kirschner MW, Kaelin WG (2004) Degradation of the SCF(Skp2) complex by misexpression of human Cdc14B phosphatase. Mol Biol Cell 13:2289–2300
