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The Emerging Role of APC/C^{Cdh1} in Development

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Abstract

The function of APC/C (anaphase-promoting complex/cyclosome) was initially implicated with the onset of anaphase during mitosis, where its association with Cdc20 targets securin for destruction, thereby allowing the separation of two duplicated daughter genomes. When combined with Cdh1, APC regulates G1/S transition and DNA replication during cell cycle. Beyond cell cycle control, results from recent biochemical and mouse genetic studies have attracted our attention to the unexpected impact of APC/C^{Cdh1} in cellular differentiation, genomic integrity and pathogenesis of various diseases. This review will aim to summarize current understanding of APC/C^{Cdh1} in regulating crucial events during development.

Keywords

APC/C; Cdh1; ubiquitylation; cell cycle; differentiation; development

1. Introduction

The critical role of UPS (ubiquitin-proteasome system) in regulating biological processes was initially appreciated in the control of cell cycle progression. Currently, the function of UPS has been broadly characterized in various cellular events, including developmental control. Results from the most recent mining of human genome have indicated the presence of hundreds of E3 ubiquitin ligases with anaphase-promoting complex (APC) and SCF complex (Skp1-Cullin 1-F-box protein) being the most well-studied. The function of APC and SCF is dependent on their upstream substrate specific factors. For example, Cdc20 and Cdh1 regulate APC while F-box proteins guide SCF complex. Various substrate factors in combination with these two E3 ligases expand their respective substrate specificity, while the substrate factors also determine the timing of degradation for the targeted proteins (Figure 1). APC/C^{Cdh1} and APC/C^{Cdc20} have distinct activity profile during cell cycle progression. In early mitosis, Cdk1 and other mitotic kinases, such as Plk1 (Polo-like-kinase 1), stimulate the activity of APC/C^{Cdc20} [1]. By contrast, phosphorylation by Cdk1 and binding by nucleocytoplasmic transport factors Rae1 and Nup98 prevent the activation of APC/C^{Cdh1}, allowing APC/C^{Cdc20} to be the major form of active APC/C [2]. The bulk of APC/C^{Cdc20}, however, is inhibited by Emi1 (Early mitotic inhibitor 1) [3] and SAC (Spindle Assembly Checkpoint). The degradation of Emi1 by SCF^{β-Trop1} (Skp1/Cullin/F-box-β-Transducin-Repeat-Containing-Protein 1) is required for the activation of APC/C^{Cdc20} [4].

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However, for APC/C^{Cdc20} to be completely active, all chromosomes have to be aligned at the metaphase plate and attached to the bipolar kinetochore-microtubule, and the SAC is satisfied. Activated APC/C^{Cdc20} targets cyclin B1 and securin for degradation to initiate the metaphase-anaphase transition [5]. In late anaphase, a drop in Cdk1 activity facilitates the dephosphorylation-dependent switching between APC/C^{Cdc20} and APC/C^{Cdh1}. Active APC/C^{Cdh1} then targets other APC/C substrates, including mitotic cyclins and cdc20, driving cellular exit from mitosis [6]. In G1, APC/C^{Cdh1} targets several substrates for degradation such as Skp2 and Tome-1, preventing premature entry of S phase [7, 8] and allowing accumulation of Wee1 for next cell cycle progression [9]. APC/C^{Cdh1} also regulates several DNA replication relevant proteins, including Geminin and Cdc6 [10] that orchestrate the assembly of pre-replication complex and initiate replication. Recent studies have now expanded our view of APC/C^{Cdh1} for its role beyond mitotic and cell cycle regulation. This review will focus on the aspect of APC/C^{Cdh1} in regulating critical events during development.

2. Mechanisms by which APC/C^{Cdh1} catalyzes substrate for ubiquitination and how APC/C^{Cdh1} is regulated

2.1 Mechanisms by which APC/C^{Cdh1} catalyzes substrate for ubiquitination

It has been well accepted that Cdh1 and Cdc20 function as substrate adaptor to recruit substrate for ubiquitination. However, the affinity between co-activator and substrate is extremely low, suggesting that APC/C core subunits may also be involved in substrate recognition. As expected, besides Cdh1, Apc10/Doc1 has been implicated in substrate recognition [11, 12]. One most recent study demonstrates that Cdh1 and Apc10/Doc1 function as the D-box (Destruction box, RxxLxxxxN) co-receptor [13]. D-box and KEN box (KENxxxxN) are two canonical destruction motifs present in most APC/C substrates [14, 15], although other less well characterized motifs, such as A-box, GxEN box, and CRY box, have also been identified [16]. Interestingly, Apc10/Doc1 does not participate in the recognition of KEN box by Cdh1, indicating that Apc10/Doc1 specifically contributes to D-box-dependent recognition. While WD40 domain mediates binding of Cdh1 to D-box, the detailed mapping of Apc10/Doc1-D-box interaction warrants further investigation. In fact, Cdh1, Apc10/Doc1, and Apc2 assemble to form a combined catalytic and substrate-recognition module. Both Cdh1 and Apc10/Doc1 connects to Apc2, while the cullin-like protein Apc2 acts as a scaffold bringing the RING finger protein Apc11 and an Ub-conjugated E2 to proximity.

In general, a polyUb chain composed of at least four Ub moieties can be recognized by proteasome as a proteolytic signal [17], although monoubiquitinations have been shown to be sufficient for proteasome-dependent degradation (e.g., p105 NF- κ B precursor) [18]. Differently linked polyUb chains specify distinct biological outcomes. K48-linked polyUb targets protein for degradation, while K63-linked polyUb acts as a nonproteolytic regulatory signal involved in DNA damage, protein trafficking, signaling activation [19]. Interestingly, human APC/C preferentially catalyzes formation of K11-linked polyUb (noncanonical chain) [20]. A two-step model has been proposed: the E2 conjugating enzyme UBCH10 and UBCH5 pre-ubiquitinate the substrate while UBE2S drives the elongation of the ubiquitin chain [21-23]. Ub modification can also be reversed by deubiquitination, indicating that the fate and function of Ub-conjugated protein reflect the totality of ubiquitination and deubiquitination. USP44 (Ubiquitin-Specific Peptidase 44) was recently identified to deubiquitinate Cdc20, leading to stabilization of Cdc20-Mad2-BubR1 complex and preventing the premature activation of APC/C [24, 25]. USP44 itself is degraded at the end of cell division. Accompanying these interesting observations, several questions need to be addressed: for example, is the degradation of USP44 responsible for SAC inactivation? Is

there any role of USP44 in addition to maintaining the SAC through deubiquitinating Cdc20? Being closely-related to Cdc20, is Cdh1 also targeted by USP44, or, if not, by other USPs?

There is mounting evidence showing that one E3 ligase can target multiple substrates. The list of substrates for APC/C^{Cdh1} is still increasing. One accompanying interesting question is how the degradation of these substrates is coordinated. One important mechanism is that APC/C^{Cdh1} exhibits different processivity to different substrates. Substrates with high affinity, such as cyclin B1 or securin, bind to APC/C^{Cdh1} for sufficient length of time, allowing the addition of long Ub chain within a single binding event [26]. By contrast, lower affinity substrates residue interact with APC/C^{Cdh1} briefly and requires multiple binding events to achieve a Ub chain recognizable by proteasome. The spatial and temporal regulation may be another mechanism underlying the differential ubiquitination of substrates by APC/C^{Cdh1}.

2.2 Regulation of APC/C^{Cdh1}

The activity of APC/C^{Cdh1} is tightly regulated for the timely degradation of multiple substrates and proper progression of cell cycle. APC/C^{Cdh1} activity is elevated in late anaphase and persists through G1-phase. Several mechanisms contribute to the regulation of APC/C^{Cdh1}, including phosphorylation of Cdh1 and its substrates, APC/C inhibitors and Cdh1 degradation.

In addition to the well-established role of Cdk-dependent phosphorylation in the regulation of Cdh1 activity through cell cycle progression, phosphatase Cdc14B has also been shown to regulate Cdh1 activity during DNA damage response. In response to genotoxic stress, Cdc14B dephosphorylates and activates Cdh1, leading to degradation of multiple APC/C^{Cdh1} substrates, including cyclin B and Plk1. As a result, DNA damage check point is activated to facilitate DNA repair and prevent mitotic entry [27]. In addition to the phosphorylation of Cdh1, phosphorylation of substrates also provides another layer of APC/C^{Cdh1} regulation. For example, CDK2-mediated phosphorylation of Skp2 disrupts its association with APC/C^{Cdh1}, leading to a gradual increase of Skp2 protein level at G1-phase. On the other hand, Cdc14B-dependent dephosphorylation promotes Skp2 degradation at the M/G1 transition [7, 8, 28].

Emi1 is an inhibitor of APC/C, antagonizing the activity of APC/C^{Cdh1} at G2 [29, 30] and G1/S transition [31]. Mechanistically, Emi1 contains a conserved D-box and ZBR (Zinc-Binding Region) motif. D-box-mediated binding of Emi1 to APC/C^{Cdh1} blocks the accessibility of substrate to APC/C^{Cdh1}, while ZBR motif inhibits APC/C E3 ligase activity [32]. Mutation of the ZBR converts Emi1 into an APC/C substrate, further validating its function as a pseudo-substrate-based inhibitor. An additional motif, called RL tail located at the C-terminus, was recently identified, which is required for interaction of Emi1 with APC/C. Likely, the RL tail functions as a docking site to promote the interactions of the D-box and the ZBR motif with APC/C and thereby inhibiting APC/C function [33].

Finally, targeting Cdh1 for degradation provides another mechanism of APC/C^{Cdh1} regulation. Cdh1 protein level is high in mitosis but it is inactivated towards late anaphase. By contrast, Cdh1 protein level is considerably lower in G1-phase, although it is active and most of it associates with APC/C. Autoubiquitination may be responsible for the low level of Cdh1 in G1 phase [34]. Cdh1 degradation also occurs in S phase. Being phosphorylated by Cdk in S phase, Cdh1 translocate from nucleus to cytosol, where it is recognized and targeted for degradation by the SCF complex, the predominant E3 ligase in S phase [35].

3. APC/C^{Cdh1} is a master G0/G1 regulator and involved in differentiation processes

Progress from recent studies has sketched a dominative role of Cdh1 in the regulation of G1 phase and quiescent G0 phase. Loss of *fzr* in *Drosophila* leads to extra embryonic epidermal cell division, which is likely caused by accumulation of mitotic cyclins in G1-phase [36]. *FZR1* mutant yeast was defective in cell cycle arrest in G1-phase after nutrient starvation [37]. The well-established function of APC/C^{Cdh1} in the maintenance of stable G0/G1 phase depends on the degradation of positive cell cycle regulators. APC/C^{Cdh1} can completely eliminate mitotic cyclins, can further inactivate Cdk1 activity by degrading Cdc25A, and can target Skp2 and Cks1 for degradation, leading to accumulation of Cdk inhibitors p21 and p27 [8]. APC/C^{Cdh1} also inhibits cyclin D1 expression by targeting the transcription factor Ets2 for degradation [38].

G0/G1 phase provides a window, where cells either exit cell cycle or enter a new cycle. Cell cycle exit can occur reversibly during periods of starvation or for stem cells that divide rarely and stay mostly in quiescent state. However, when cells are directed to a specific fate during terminal differentiation, they irreversibly exit cell cycle. Loss of Cdh1 has been shown to cause reentry into cell cycle followed by apoptotic cell death in postmitotic neurons. Terminal differentiation is tightly regulated by transcriptional events mediated by opposing transcriptional activators and repressors. Degradation of repressors allows cells to rapidly activate genes in response to differentiation cues. Multiple repressors, including SnoN, have been shown to be targeted by APC/C^{Cdh1} for degradation, allowing APC/C^{Cdh1} to fulfill its differentiation-regulated functions (Figure 2).

4. Emerging role of APC/C^{Cdh1} in developmental processes

Previous observations from the laboratories of Jan M. Peter and Marc W. Kirschner have suggested a role for APC/C^{Cdh1} in developmental control [39, 40]. Evidence that APC/C^{Cdh1} mediates TGF- β signaling further indicates the importance of APC/C^{Cdh1} in coordinating cellular proliferation and differentiation [39, 41-44]. The recent effort in mouse genetic analysis has shown the relevance of APC in association with Cdc20 or Cdh1 in development and pathogenesis of certain diseases. Results from the targeted deletion of Cdc20 in mouse embryo of arrest in metaphase at the two-cell stage indicate the involvement of APC/C^{Cdc20} in mammalian embryogenesis [45]. The role of Cdc20 in mitosis is not redundant with that of Cdh1, consistent with the notion that Cdh1 mainly functions as the master regulator of G0/G1 phase [46]. Most recently, Cdh1 knockout mice have been generated [47]. Similarly to *Fzr* inactivation in *C. elegans* and *Drosophila* [48, 49], deletion of mouse *Fzr* results in embryonic lethality [47]. However, rather than from embryonic defects, the lethality is due to placental malfunction, which is caused by defective endoreduplication of placental trophoblasts. The biological significance of endoreduplication in placental trophoblasts is thought to increase DNA content that is needed to sustain the mass production of proteins and high metabolic activity required for embryogenesis [50]. The mechanism for the regulation of endoreduplication by Cdh1 remains unknown. One possibility is that, similar to DNA damage-induced Cdh1 activation, Cdc14B-dependent dephosphorylation activates Cdh1 in G2. Cdh1, in turn, prevents mitotic entry through targeted degradation of Plk1 and subsequent checkpoint activation. Another possibility is that the release of inhibition of Cdh1 by Emil1 and securin leads to the activation of Cdh1 at G2-phase. Being a substrate of APC/C^{Cdh1}, securin has been shown to inhibit APC/C^{Cdh1} activity through competition with other APC/C^{Cdh1} substrates [51]. One recent study in *Arabidopsis thaliana* shows that atypical E2F transcriptional factor E2Fe/DEL1 controls the timing of endoreduplication by regulating the expression of the Cdh1 orthologs CCS52A2. Interestingly, a typical mammalian E2F7 was found to associate with

the promoter of Cdh1 [52]. Whether E2F7 is also involved in the regulation of endoreduplication by Cdh1 in placental trophoblasts remains unknown. Notably, the placental defect can be rescued when Cdh1 is specifically deleted in the embryo but not in the placenta. However, these mice survive for only a few days after birth. Although the cause of death remains elusive, the shortened lifespan of mice implies that Cdh1 plays a critical role in the developmental process.

4.1 Oogenesis

Two critical stages of mammalian oocyte regulation are prophase I (equivalent to G2) arrest and the progression through MI (meiosis I) to fertilizable eggs. Prophase I arrest is important for sustaining oocyte pool in the ovary. The maintenance of prophase I arrest is thought to be mediated by PKA (Protein Kinase A). PKA inhibits Cdk1 activity via activation of Cdk1-inhibiting kinase Wee1 and suppression of Cdk1-activating phosphatase Cdc25 [53]. The proteolysis of cyclin B, the binding partner of Cdk1, also has critical role in orchestrating prophase I arrest [54]. Notably, regulation of cyclin B protein levels needs to be precise, which otherwise would make oocytes hormonally insensitive [55]. Nevertheless, the precise mechanism for the regulation of cyclin B1 remains unknown. Likely, the regulated cyclin B1 levels depend on the balance between active Cdh1, for example by Cdc14B [56], and inactive Cdh1, for example by Emi1 and Securin [51, 57]. Interestingly, the mechanisms governing prophase I arrest and meiotic resumption share features with DNA-damage-induced mitotic G2 arrest and mitotic recovery.

In addition to the maintenance of meiotic prophase I arrest, APC/C^{Cdh1} also plays a role in prometaphase I after meiotic resumption. APC/C^{Cdh1} is required for homologue congression. The timing of activation of APC/C in meiosis I by its co-activator Cdh1 and Cdc20 is a reversal in comparison with somatic mitosis. APC/C^{Cdh1} is activated first, during prophase I and prometaphase I, while APC/C^{Cdc20} is activated as a result of Cdk1-mediated switch during anaphase I, targeting securin and cyclin B1 for degradation and leading to meiotic exit [58]. Notably, the surveillance mechanism known as SAC also exists in oocytes to modulate the metaphase I-to-anaphase I transition [59, 60]. In contrast to mitosis, BubR1 has additional functions in MI separate from its SAC role. BubR1 can maintain the stability of Cdh1 and thus is required for the maintenance of prophase I arrest and progression of prometaphase I [61]. BubR1-depleted oocytes can bypass the prophase I arrest, reentry into MI, and then arrest at prometaphase I. The failure of anaphase I is caused by overaccumulation of securin followed by the inhibition of APC/C^{Cdc20}, while the securin accumulation is attributed to diminished APC/C^{Cdh1} activity. Given the critical role of APC/C^{Cdh1} in meiotic phase I arrest and prometaphase progression, Cdh1 deletion would affect mouse fertility by reducing prophase I-arrested oocyte pool and the yield of fertilizable eggs.

4.2 Hematopoiesis

The microenvironment, or niche, plays a pivotal role in self-renewal and differentiation of adult stem cells [62, 63]. HSCs (Hematopoietic Stem Cells), one of the best characterized adult stem cells, are found to be predominantly located in hypoxic bone marrow niche [64]. To adapt to the severe hypoxic condition, LT-HSCs (Long-term HSCs) have been shown to develop unique metabolic phenotype utilizing cytoplasmic glycolysis instead of mitochondrial oxidative phosphorylation to generate ATP [65].

One recent finding is that APC/C^{Cdh1} regulates glycolysis through degrading Pfkfb3 (6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase, isoform3). Pfkfb3 regulates the rate of glycolysis by generating F2, 6P (2) (fructose-2, 6-bisphosphate), which is the most potent activator of PFK1 (6-phosphofructo-1-kinase), a master regulator of glycolysis. Inactivation of APC/C^{Cdh1} enables Pfkfb3 to upregulate glycolysis, thus favoring cell proliferation.

Given the negative regulation of glycolysis by APC/C^{Cdh1} in many types of cells, the role of APC/C^{Cdh1} in HSCs will need further attention. Our group recently applied RNA interference technique to knockdown Cdh1 in HSCs and utilized CAFC (Cobble Stone Area-Forming Cell) assay to evaluate the subsequent effect (unpublished data). The results show that the number of cobblestone-like structures is surprisingly higher in Cdh1-KD cells. The striking phenotype provides a rationale to test the hypothesis both *in vivo* and *in vitro* that inactivation of APC/C^{Cdh1} in HSCs leads to upregulation of glycolysis, which facilitates survival by HSCs in hypoxic niche. In fact, hypoxic or anoxic insults would invariably eliminate differentiated cells that rely on oxidative metabolism.

Additional evidences supporting a role for APC/C^{Cdh1} in hematopoiesis comes from Cdh1 knockout mice. Cdh1 heterozygous mice can develop B-cell lymphoma and myelodysplastic disorder [47]. Although how APC/C^{Cdh1} regulates hematopoiesis remains to be investigated, results from several studies suggest that targeted degradation of Id protein could be one mechanism. (1) Id protein modulates proliferation and differentiation of various types of cells, such as neural or hematopoietic cells [66]. (2) APC/C^{Cdh1} targets Id2 for degradation in neurons and inhibits axon growth [67]. (3) Id1, but not Id3, is essential for the LT-HSC maintenance and hematopoietic development [68]. The balance between Id1 and E-protein regulates myeloid-versus-lymphoid lineage commitment [69]. Id2 intrinsically inhibits lymphoid development [70] and may also be involved in myeloid lineage commitment. (4) Expression of Id1 and Id2 may contribute to the development of myeloid malignancies through enhanced proliferation and inhibited differentiation of myeloid progenitors [66].

4.3 Neurogenesis

APC/C was suggested to be a crucial player in nervous system, where appreciable levels of Cdh1 and APC/C subunits are always detected in the postmitotic neurons [40]. Evidences indicate that APC/C^{Cdh1} and APC/C^{Cdc20} could regulate distinct aspects of neuronal development and maturation. APC/C^{Cdh1} restricts axon growth and controls its patterning in mammalian brain, while APC/C^{Cdc20} orchestrates presynaptic differentiation, the late phase of axon morphogenesis, and dendrite growth. APC/C^{Cdh1} has also been shown to regulate synapse development in invertebrates [71]. Mechanistically, targeted degradation of SnoN [72, 73] and Id2 [67] are involved in APC/C^{Cdh1}-regulated axon growth and patterning. Interestingly, as a transcription factor, SnoN may activate or repress transcription depending on cell type and targeted gene. In contrast to its widely-explored function being a transcription repressor, SnoN has a transcriptional activating role in neurons [74]. Ccd1, one of SnoN targets, has been reported to mediate SnoN-dependent axon growth. In addition to the cell-intrinsic regulation of axonal morphogenesis, APC/C^{Cdh1}-SnoN has also mediated the response of neuron to extrinsic cue, such as TGF- β .

APC/C^{Cdh1} also controls bioenergetics and antioxidant status of neurons. Cdh1 is highly expressed in neuron and inhibits glycolysis by targeting Pfkfb3 for degradation. As a result, neurons use glucose, not for bioenergetics purpose, but to maintain their antioxidant status through the pentose phosphate pathway. Inhibition of Cdh1 would result in oxidative stress and apoptotic death [75]. Besides glycolysis regulation, APC/C^{Cdh1} functions to maintain the stable G0/G1, preventing the cell cycle re-entry of post-mitotic neuron, which otherwise would cause apoptotic cell death [76].

One most recent study has implicated APC/C^{Cdh1} in the assembly of nervous system [77]. During development, glial cells often follow extending axons, suggesting that axonal outgrowth and glial migration are precisely coordinated. A subcellular gradient of adhesiveness has been proposed as the coordinating mechanism. APC/C^{Cdh1} functions to establish a graded distribution of Fas2 in neurons. Axonal Fas2 interacts homophilically with a glial isoform of Fas2 and mediates neuron-glial adhesion. Glial migration is initiated

along axonal segments that have low levels of Fas2 but stalls in axonal domains with high levels of Fas2.

4.4 Lens and muscle cell differentiation

Most recent study shows that APC/C^{Cdh1} is expressed in undifferentiated hESCs (human embryonic stem cells) but are kept inactive by phosphorylation and Emi1. During differentiation, Emi1 dramatically declines, leading to APC/C^{Cdh1} activation. The dynamic nature of APC/C^{Cdh1} implies that APC/C^{Cdh1} plays a role in hESCs differentiation [78]. In addition to the above-mentioned organ, APC/C^{Cdh1} is also involved in the development of other organs. Studies from our group indicate that APC/C^{Cdh1} plays a critical role in the differentiation of lens [42] and muscle cell [79]. The APC/C^{Cdh1}-regulated lens differentiation is mediated by TGF- β -induced destruction of SnoN, which shares the common feature with axon growth in response to extrinsic TGF- β signaling [73]. Targeted degradation of Skp2 and Myf5 by APC/C^{Cdh1} is thought to facilitate myoblast differentiation, while downregulation of Skp2 leads to stabilization of p21 and p27 that are required for cell cycle withdrawal and initiation of differentiation and destruction of Myf5 regulates the myogenic fusion.

5. Conclusion

APC/C^{Cdh1} has multiple roles in somatic cell cycle, including controlling mitotic exit and maintaining stable G0/G1 phase. Recent research has implicated APC/C^{Cdh1} in the regulation of developmental processes (Figure 3). The critical role of APC/C^{Cdh1} in developmental regulation depends on its function in cell cycle (endoreduplication and meiosis) and beyond cell cycle (differentiation and other post-mitotic processes). The increasing list of APC/C^{Cdh1} substrates provides mechanistic insight into the function of APC/C^{Cdh1} in developmental control. Although APC/C^{Cdh1} KO mice provide compelling evidence to support the role of APC/C^{Cdh1} in developmental processes, several important questions remain to be addressed. (1) APC/C^{Cdh1} has been shown to control synaptic differentiation in worms and flies through regulating Liprin α and glutamate receptor subunits [80, 81]. Whether a similar mechanism exists for mammalian neurons and whether APC/C^{Cdh1} contributes to the abnormalities of learning and memory observed in Cdh1 KO mice remain to be determined. (2) The role of APC/C^{Cdh1} in hematopoiesis remains poorly understood. (3) Extrinsic cues, such as TGF- β , that may interplay with the cell-intrinsic functions of APC/C^{Cdh1} in developmental processes, such as neurogenesis and lens development need to be identified. (4) Conditional KO strategies are required to more specifically elucidate the functions of APC/C^{Cdh1} in developmental processes. Finally, the atomic resolution structure of APC/C is required for future studies to better understand the function of APC/C^{Cdh1}. The complete understanding of APC/C^{Cdh1} would facilitate the design of drugs specifically modulating APC/C^{Cdh1} function, which may have therapeutic implications for diverse developmental disorders.

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Figure 1.
Function of APC inside and outside of cell cycle in comparison with SCF complex.

Figure 2.
Coordination between cell cycle and cellular differentiation by APC^{Cdh1}.

Figure 3.
Summary of the emerging role for APC^{Cdh1} in regulating critical processes during development.