The APC/C ubiquitin ligase: from cell biology to tumorigenesis

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The ubiquitin proteasome system (UPS) is required for normal cell proliferation, vertebrate development, and cancer cell transformation. The UPS consists of multiple proteins that work in concert to target a protein for degradation via the 26S proteasome. Chains of an 8.5-kDa protein called ubiquitin are attached to substrates, thus allowing recognition by the 26S proteasome. Enzymes called ubiquitin ligases or E3s mediate specific attachment to substrates. Although there are over 600 different ubiquitin ligases, the Skp1–Cullin–F-box (SCF) complexes and the anaphase promoting complex/cyclosome (APC/C) are the most studied. SCF involvement in cancer has been known for some time while APC/C's cancer role has recently emerged. In this review we will discuss the importance of APC/C to normal cell proliferation and development, underscoring its possible contribution to transformation. We will also examine the hypothesis that modulating a specific interaction of the APC/C may be therapeutically attractive in specific cancer subtypes. Finally, given that the APC/C pathway is relatively new as a cancer target, therapeutic interventions affecting APC/C activity may be beneficial in cancers that are resistant to classical chemotherapy.

Keywords: ubiquitin, cell cycle, differentiation, cancer, ubiquitin ligase, cancer therapy

INTRODUCTION

Any discussion of the anaphase promoting complex/cyclosome (APC/C) pathway as a possible therapeutic target has to start with the question of what makes APC/C unique among the many ubiquitin ligases present in human cells. On one level APC/C is mechanistically similar to the Skp1–Cullin–F-box (SCF) ubiquitin ligases where there are core subunits and an adaptor protein that directly binds to a substrate. In SCFs, the four subunits are Skp1 (scaffold protein), Cul1 (scaffold protein), RING-finger component (Rbx1), and the variable adaptor protein or F-box protein that recognizes substrates (Zheng et al., 2002). In APC/C there are 13 subunits as well as variable adaptor proteins termed Cdc20 (or Fizzy; Fzy), Cdh1 (or Fizzy-related; Fzr), Cortex, Ama1, or Mfr1

(Acquaviva and Pines, 2006; Hutchins et al., 2010; Kops et al., 2010). However, beyond these similarities regarding adaptors and subunits present in APC/C and SCF ligases, large differences in size and structure exist between these two types of ligases. By contrast to SCF ubiquitin ligases, there is only limited knowledge regarding APC/C structure mainly because the enormous size and complexity of the holoenzyme present significant challenges for structure determination at the atomic level. The first structural insights into the APC/C was obtained by cryo-EM of complexes purified from human cells, *Xenopus laevis* egg extracts, and budding yeast (Gieffers et al., 2001; Dube et al., 2005; Passmore et al., 2005). 3D modeling showed that in all cases the APC/C is an asymmetric triangular complex (200 by 230 Å in size), composed of an outer wall and an internal cavity. Cdh1 and the Cullin domain of the Apc2 subunit are located on the outside of the complex, making it plausible that ubiquitination reactions occur on the outside and not inside the cavity. An emerging view of the APC/C is that of a four-part enzyme composed of a structural arm or scaffolding unit made of Apc1, Apc4, and Apc5, a catalytic arm consisting of Apc2, Apc11, and Doc1 (or Apc10), a tetratricopeptide repeat (TPR) arm made of Cdc23, Cdc16, and Cdc27, which mediates binding to activators and coactivators (Cdc20, Cdh1, Cortex). Other subunits such as Cdc26, Apc9, and Swm1 stabilize the TPR arm (Schwickart et al., 2004; Thornton and Toczyski, 2006). The TPR subunits have 12–15 copies of the 34-amino acid long TPR. They facilitate interactions between subunits and the assembly of multisubunit complexes (Zachariae and Nasmyth, 1999). A pseudo-atomic model of the yeast APC/C obtained by reconstitution studies of the holoenzyme and its subcomplexes has revealed that the TPR arm along with the structural

arm coordinate the juxtaposition of the catalytic arm and the TPR phosphorylation sites relative to the coactivators, substrates, and regulators (Schreiber et al., 2011).

A previously unidentified APC/C subunit, Apc16, was reported recently (Hutchins et al., 2010; Kops et al., 2010). It is a small protein of 11.7 kDa in size encoded by Chromosome 10 open reading frame 104 (C10orf104) in humans. Apc16 may facilitate Cdc27 hyperphosphorylation, although it is not essential for assembly of the holocomplex (Kops et al., 2010). Therefore, the APC/C is composed of multiple subunits, some of which are newly discovered. However, the minimum ubiquitin ligase module of the APC/C that can catalyze ubiquitination is comprised of just two subunits – the Apc2 Cullin subunit and the Apc11 RING subunit (Gmachl et al., 2000; Leverson et al., 2000; Tang et al., 2001), which are analogous to the Cullin and Rbx1 subunits of the SCF complex (Barford, 2011). Thus, while we still do not have a complete understanding of APC/C structure, we are beginning to understand the general architecture of the complex, and possibly achieve an atomic level resolution of APC/C subcomplexes. These subcomplexes may provide multiple binding sites for small molecules that would perhaps make APC/C unique among ubiquitin ligases as a therapeutic target.

APC/C ACTIVITY

Another attractive aspect of the APC/C as a drug target is that it binds a unique set of enzymes required for transferring ubiquitin to substrates. The process of ubiquitination begins with the ubiquitin-activating enzyme E1 binding to and activating ubiquitin in an ATP-dependent manner. This activated ubiquitin is then transferred to a ubiquitin-conjugating enzyme or E2. The ubiquitin ligases or E3 enzymes then associate with E2s to catalyze the ubiquitin transfer to the ε-amino group of lysine residues on substrate proteins (Ye and Rape, 2009). Multiple ubiquitin molecules can be linked together in different ways to form polyubiquitin chains that satisfy different objectives. In yeast, chains linked via Lysine 48 of ubiquitin (K48 chains) are a "proteolytic signal" whereas those linked via Lysine 63 (K63 chains) function as molecular scaffolds. In higher eukaryotes, the APC/C is known to build atypical K11-linked polyubiquitin chains on its substrates in association with its unique E2 partner, Ube2C (or UbcH10; Wickliffe et al., 2011b). Ube2C only initiates chain formation, however. Chain elongation is carried out by a K11-specific E2 called Ube2S (or E2–EPF) that works with both APC/C^Cdc20 and APC/C^Cdh1 (Garnett et al., 2009; Wu et al., 2010; Wickliffe et al., 2011a). The importance of this dual regulation of APC/C activity via Ubch10 and Ube2S is underscored by the finding that removing K11-specific E2s causes defects in spindle assembly and mitotic progression (Williamson et al., 2009).

One of the most attractive means of attenuating APC/C activity pharmacologically is by modulating the adaptor protein–substrate binding reaction. Early studies in yeast identified the Cdc20 and Cdh1 substrate binding adaptor proteins as required for APC/C activity (Visintin et al., 1997). Subsequent studies in multiple experimental systems demonstrated the biochemical requirements for these adaptors to bind their substrates (Fang et al., 1998). Although exceptions exist, Cdc20 and Cdh1 bind substrates containing the sequence elements RXXLXXXXN/D/E or destruction
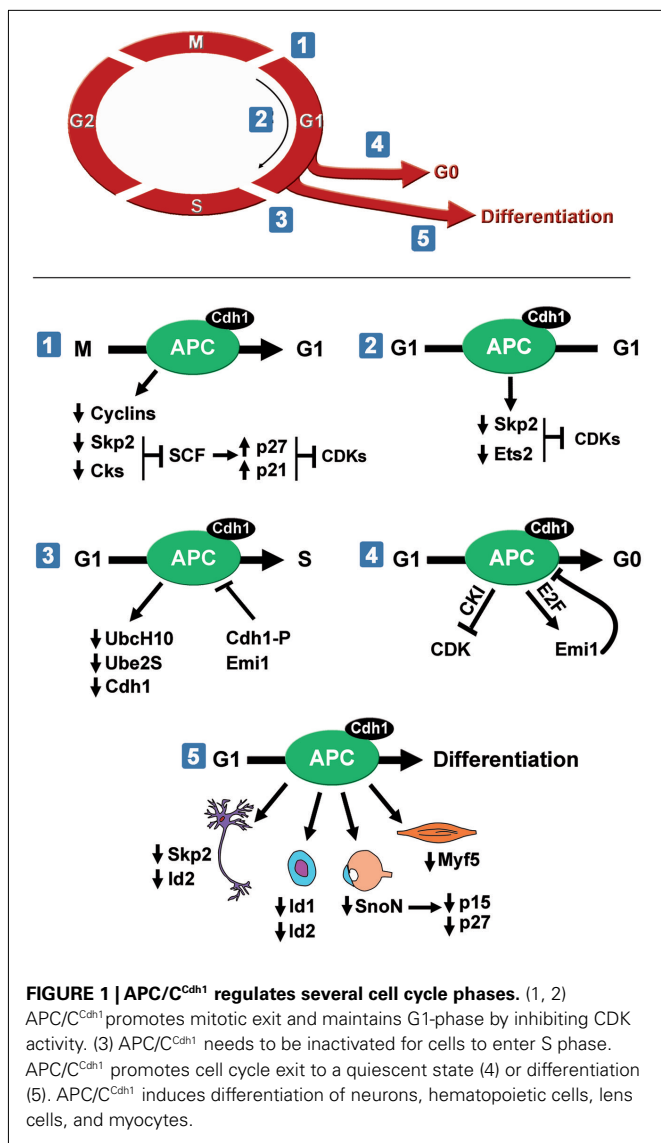
boxes (D-boxes), while Cdh1 can also bind substrates containing KEN sequences (Glotzer et al., 1991; Pfleger and Kirschner, 2000). Substrate binding initiates ubiquitination mediated by APC/C^Cdc20 or APC/C^Cdh1. However, APC/C^Cdc20 or APC/C^Cdh1 mediated substrate binding is controlled during the cell cycle using an overlapping series of regulatory mechanisms. Inhibitory complexes control APC/C activity during the cell cycle, thus limiting its activity to defined temporal windows (for reviews see Manchado et al., 2010; Qiao et al., 2010; Pines, 2011). One of the most important examples of this is the exquisite control of APC/C^Cdc20 activity during mitosis. In early mitosis, APC/C^Cdc20 activity is curtailed by the spindle assembly checkpoint (SAC), which monitors the attachment of kinetochores to the mitotic spindle. An inhibitory complex containing Mad2, Bub3, and BubR1 proteins sequesters Cdc20 and renders it unable to bind substrates (Kim and Yu, 2011). After the checkpoint is switched off, this complex is released from APC/C^Cdc20, which initiates the metaphase to anaphase transition by mediating degradation of key proteins such as securin, shugoshin, and cyclin B1 (Kim and Yu, 2011). Securin and cyclin B1 degradation activates separase, which cleaves the cohesin complex that holds sister chromatids together while shugoshin destruction relieves sister chromatid cohesion at the centromere (Wang and Dai, 2005). These reactions are essential for the metaphase to anaphase transition, which is inhibited when APC/C activity is abrogated pharmacologically or by siRNA depletion or genetic disruption of *Cdc20* (Huang et al., 2009; Manchado et al., 2010; Zeng et al., 2010). Cells lacking APC/C^Cdc20 eventually undergo mitotic catastrophe and die in a manner reminiscent of microtubule inhibition (Zeng et al., 2010). However, APC/C inhibitory molecules may have the added advantage that they will not have the usual off-target effects of microtubule inhibition well-known during chemotherapy treatment (Huang et al., 2009; Manchado et al., 2010).

APC/C^Cdh1 CONTROLS SEVERAL CELL CYCLE TRANSITIONS

Small molecules that inhibit substrate ubiquitination via APC/C^Cdc20 also reduce APC/C^Cdh1 activity (Zeng et al., 2010). Since the APC/C^Cdh1 window of activity during the cell cycle is larger than that of APC/C^Cdc20, it may be easier to modulate APC/C^Cdh1 specific pathways necessary for growth of a particular cancer cell. APC/C^Cdh1 controls mitotic exit and maintains the G1-phase in cycling cells (**Figure 1**). Outside the cell cycle, APC/C^Cdh1 is required for quiescence, cell cycle exit, and differentiation (**Figure 1**). These multiple roles suggest the presence of distinct upstream regulatory and signaling pathways controlling APC/C^Cdh1 within temporal or developmental windows. Importantly, these pathways will likely provide unique interactions with APC/C that can be targeted pharmacologically.

APC/C^Cdh1 IS REQUIRED FOR MITOTIC EXIT AND G1 MAINTENANCE

APC/C^Cdh1 targets multiple substrates for degradation during mitosis (**Figure 1**). Foremost among these are the mitotic cyclins, whose degradation ablates cyclin-dependent kinase 1 (CDK1) activity (Brandeis and Hunt, 1996; Irniger and Nasmyth, 1997). APC/C also reduces activity of multiple CDKs by initiating degradation of two components of the SCF ubiquitin ligase, the F-box protein Skp2 and an accessory protein, Cks1 (Bashir et al., 2004;

FIGURE 1 | APC/C^{Cdh1} regulates several cell cycle phases. (1, 2) APC/C^{Cdh1}promotes mitotic exit and maintains G1-phase by inhibiting CDK activity. (3) APC/C^{Cdh1} needs to be inactivated for cells to enter S phase. APC/C^{Cdh1} promotes cell cycle exit to a quiescent state (4) or differentiation (5). APC/C^{Cdh1} induces differentiation of neurons, hematopoietic cells, lens cells, and myocytes.

Wei et al., 2004). Degradation of these two substrates raises the levels of the cyclin-dependent kinase inhibitors p27^{Kip1} and p21^{Cip1}, which are normally targeted for degradation in an SCF^{Skp2} and Cks1 dependent manner (Ganoth et al., 2001; Bornstein et al., 2003). CDK inhibitors associate with specific cyclins and CDKs, preventing them from binding to ATP, and hence blocking their catalytic activity. Thus, high p27^{Kip1} and p21^{Cip1} levels maintain an early G1 state by reducing CDK activity. Another mechanism to promote G1 by reducing CDK activity involves APC/C^{Cdh1} mediated inhibition of an activator of S phase entry, cyclin D1. APC/C^{Cdh1} initiates degradation of the transcription factor Ets2 (Li et al., 2008), which normally controls cyclin D1 levels (Albanese et al., 1995). Consistent with these findings, depletion of Cdh1 by siRNA stabilizes Skp2 and Ets2, resulting in p21^{Cip1} and p27^{Kip1} degradation and cyclin D1 elevation in G1, followed by premature S phase entry (Wei et al., 2004; Li et al., 2008) and increased proliferation (Bashir et al., 2004). Thus, APC/C^{Cdh1} function during mitotic exit is coupled to G1 maintenance. It initiates a sharp

decrease in CDK1 activity during mitotic exit by targeting the mitotic cyclins for destruction and subsequently remains active in early G1 to ensure that they remain inactive. In addition, it ensures that other cyclin-dependent kinases, namely CDK2/cyclin E, CDK2/cyclin A, CDK4/cyclin D, and CDK6/cyclin D are inactive since it maintains high p27^{Kip1} levels and low cyclin D1 levels through Skp2 and Ets2 degradation.

One question that immediately arises from these studies is that if APC/C keeps CDKs inactive in early G1, how do cells eventually reach S phase. The answer lies in the multiple mechanisms that decrease APC activity (**Figure 1**). For instance, the ubiquitination of the APC/C-specific ubiquitin-conjugating enzyme (E2) UbcH10 by APC/C^{Cdh1} provides a negative feedback mechanism that eventually dampens APC/C^{Cdh1} activity (Rape and Kirschner, 2004; Rape et al., 2006). Further, Cdh1 is inactivated by both phosphorylation and degradation (Lukas et al., 1999; Listovsky et al., 2004; Benmaamar and Pagano, 2005). Finally, E2F activates the transcription of the APC/C pseudo-substrate early mitotic inhibitor-1 (Emi1)/Rca1 in late G1, which inhibits APC/C^{Cdh1} activity (Hsu et al., 2002). These distinct mechanisms ensure that APC/C^{Cdh1} activity remains low from late G1 until the subsequent metaphase when it is activated via reduction of CDK and Emi1 activity (Kotani et al., 1998; Hsu et al., 2002; **Figure 1**).

APC/C^{Cdh1} CONTROLS PRE-REPLICATION COMPLEX FORMATION

One of the main reasons APC/C^{Cdh1} activity must remain low during S phase is that it is an inhibitor of pre-replication complex formation required for S phase entry (Diffley, 2004). APC/C^{Cdh1} controls the formation of the pre-replication complexes by modulating levels of three major regulators of the formation of the complex: Orc1, Cdc6, and geminin. For DNA replication to proceed, cells need to alternate between periods of low CDK activity and low geminin levels, in which the pre-replicative complexes (preRCs) are assembled; and periods of high CDK activity and high geminin levels in which origin firing and DNA replication occurs (McGarry and Kirschner, 1998; Petersen et al., 2000; Araki et al., 2003). APC/C^{Cdh1} is crucial to properly regulate the switch between these two states. For instance, Orc1 and Cdc6 are degraded via APC/C^{Cdh1} during early G1 (Petersen et al., 2000; Araki et al., 2003). Further, geminin levels are tightly controlled by APC/C^{Cdh1}. Geminin prohibits initiation of DNA replication at inappropriate times of the cell cycle by preventing MCM recruitment at the replication origins. During G1 the APC/C is active and as a consequence, geminin concentration is low. At the G1–S transition, APC/C is inactivated and geminin begins to accumulate. However, geminin concentration is not sufficient to inhibit a first wave of preRC formation and DNA replication begins. As S phase progresses, geminin accumulates and inhibits subsequent recruitment of MCMs to the replication origins (McGarry and Kirschner, 1998), and therefore re-duplication is avoided (McGarry and Kirschner, 1998; Wohlschlegel et al., 2000).

APC/C^{Cdh1} PROMOTES CELL CYCLE EXIT AND QUIESCENCE

Multiple studies suggest that a major APC/C^{Cdh1} function outside of the cell cycle is limiting CDK activity required for cell cycle progression (Qiao et al., 2010). APC/C^{Cdh1} regulates CDK inhibitors that reduce CDK activity and initiate cell cycle exit. Adding a

second layer of regulation to APC/C^{Cdh1} activity, Binné et al. (2007) connected retinoblastoma protein (pRb) to APC/C^{Cdh1}, Skp2, and CDK inhibitor dependent cell cycle exit. These studies demonstrated that hypophosphorylated pRb associates with the APC/C specifically when activated by Cdh1, thus promoting Skp2 degradation and accumulation of p27^{Kip1} and p21^{Cip1}. This important finding linked extracellular signaling mechanisms, which normally control pRb activity to APC/C dependent degradation of Skp2 and initiation of cell cycle exit.

Once cells have exited the cell cycle, APC/C activity is required to maintain quiescence or differentiation. For instance, APC^{Cdh1} inactivation by deleting its Apc2 subunit in adult hepatocytes induced these otherwise quiescent cells to re-enter the cell cycle (Wirth et al., 2004). Similarly, APC^{Cdh1} has also been proposed to block postmitotic differentiated neurons from inappropriate cycling and apoptosis (Almeida et al., 2005; Jackson, 2006).

APC/C^{Cdh1} REGULATES CELL CYCLE EXIT AND CELL DIFFERENTIATION

APC/C^{Cdh1} activity promotes cell cycle exit and differentiation since Cdh1 depletion reduces differentiation of muscle, lens, hematopoietic, and neuronal cells (Lasorella and Iavarone, 2006; Li et al., 2007; Wu et al., 2007; Garcia-Higuera et al., 2008). Although our knowledge of the involvement of APC/C^{Cdh1} in the differentiation of other tissues awaits further investigation, its critical function in the degradation of cell cycle proteins suggests it likely plays relevant roles in linking quiescence and differentiation in most cell types. Further, since cancer progression is often thought to involve a dedifferentiation process (Daley, 2008; Trosko, 2009), understanding APC/C's involvement in normal cell cycle exit and differentiation will give us clues as to how APC/C regulation or substrate targeting may be misregulated during tumorigenesis.

Neuronal differentiation

Following a period of proliferation, neural progenitors differentiate into postmitotic neurons. Since Cdh1 levels are (Gieffers et al., 1999; Stegmuller and Bonni, 2005) higher in postmitotic neurons relative to their neural progenitors (Yao et al., 2010), APC/C^{Cdh1} may play a role in neuronal cell cycle exit. Consistent with this notion, an increase in APC/C^{Cdh1} activity and a decrease of APC/C^{Cdh1} substrates has been observed during terminal differentiation (Almeida et al., 2005; Yao et al., 2010). By contrast, upregulation of APC/C^{Cdh1} substrates has been described in human neural tumors, suggesting that APC/C^{Cdh1} activity is attenuated under these conditions (Lasorella and Iavarone, 2006; Eckerle et al., 2009).

Inhibitor of DNA binding 2

One of the targets that couples APC/C^{Cdh1} activity with neuronal differentiation is inhibitor of DNA binding 2 (Id2, also known as inhibitor of differentiation 2). In the developing nervous system, Id2 has been shown to inhibit the activity of neurogenic basic helix–loop–helix (bHLH) transcription factors required for neuronal differentiation (Yokota, 2001; Perk et al., 2005; Rothschild et al., 2006; Jung et al., 2010). APC/C^{Cdh1} targets Id2 for destruction, which couples cell cycle exit, differentiation, and axonal growth during the differentiation of diverse neuronal types (Lasorella and Iavarone, 2006; Yao et al., 2010). Thus, Id2 protein

downregulation via proteolysis is essential for neuronal differentiation, suggesting that deregulation of Id2 destruction may underlie neural tumors.

Deregulated Id2 expression prevents cell cycle arrest via a wide range of signals (Lasorella et al., 2002; Kowanetz et al., 2004; Baghdoyan et al., 2005). Id2 downregulation via degradation allows the bHLH transcription factor E47 levels to increase and subsequently promote neural cell differentiation through induction of the CDK inhibitor p57^{Kip2} in the developing mouse brain (Rothschild et al., 2006; Tury et al., 2011). Similarly, decreasing Id2 levels increases expression of known mediators of neuronal differentiation such as Hes1 and Ascl1 (Mash1) transcription factors (Havrda et al., 2008) and NeuroD/E47 (Jung et al., 2010). Under certain experimental conditions, ectopic Id2 is able to drive terminally differentiated cells back into the cell cycle (Chaudhary et al., 2005). Importantly, the observation that the most aggressive tumors frequently contain the highest levels of Id proteins raises the possibility that deregulating Id protein stability by APC/C^{Cdh1} might also contribute to Id accumulation in cancer.

Skp2

The APC/C substrate Skp2 controls the G1 to S transition by eliminating numerous regulatory proteins that inhibit S phase entry (Reed, 2008). The SCF^{Skp2} target p27^{Kip1} plays a large role in cell cycle exit and differentiation, particularly neuronal differentiation (Durand et al., 1998; Vernon et al., 2003; Tarui et al., 2005; Nguyen et al., 2006, 2007). Genetic disruption of p27^{Kip1} causes a general increase in cell proliferation (Fero et al., 1996; Carruthers et al., 2003), including neurogenesis in the cortex and spinal cord (Nguyen et al., 2007; Li et al., 2009). Control of p27^{Kip1} is dual, subject to the accumulation of both cyclin-CDK complexes, which promote its phosphorylation, and Skp2, which promote the ubiquitination of phosphorylated p27^{Kip1} (Carrano et al., 1999; Montagnoli et al., 1999). Harmey et al. (2009) described an essential role for APC/C^{Cdh1} in cerebellar granule progenitors by mediating Skp2 destruction, thus coordinating cell cycle exit and terminal differentiation. Similar studies uncovered APC/C^{Cdh1}–Skp2 dependent differentiation of human embryonic stem cells (Bar-On et al., 2010). Collectively, these data suggested that two well-known inducers of neuronal differentiation, nerve growth factor (NGF), and retinoic acid, hyperactivate APC/C^{Cdh1}. NGF rapidly induced APC/C^{Cdh1} activity and promoted degradation of APC substrates, including cyclin B1 and the F-box protein Skp2 (Harmey et al., 2009). Similarly, retinoic acid promoted neuronal differentiation through increasing APC/C^{Cdh1} activity (Cuende et al., 2008; Yao et al., 2010). Further, retinoic acid induced nuclear accumulation of Cdh1, enhancing APC/C^{Cdh1} activity, Skp2 destabilization, and p27^{Kip1} accumulation (Cuende et al., 2008) by reducing expression of Rae1, a nuclear export factor that limits APC/C^{Cdh1} activity in mitosis (Yao et al., 2010). Similar to NGF and retinoic acid, bone morphogenetic protein 2 (BMP2) promotes cell cycle arrest via downregulation of Skp2 and accumulation of p27^{Kip1} in a neuroblastoma cell line (Nakamura et al., 2003). Thus, Skp2 degradation via APC/C^{Cdh1} is linked to neuronal differentiation and various signaling pathways. Disruption of signaling pathways controlling the APC/C–Skp2 axis during neuronal differentiation may lead to disruption of homeostasis. Consistent with this

possibility, reduced Skp2 and cyclin B1 expression has been seen in a transgenic model of Down syndrome where alteration of cell cycle rate and reduction of neurogenesis in the cerebellum was described (Contestabile et al., 2009). Moreover, *Skp2* transcript levels gradually increase with the aggressiveness of neuroblastoma subtype (Westermann et al., 2007), making the regulation of Skp2 by APC/C^{Cdh1} an attractive target in tumorigenesis.

Muscle cell differentiation

Myogenesis is a multistep process that sequentially requires the proliferation of committed myoblasts, the differentiation of myoblasts into postmitotic myocytes, and finally fusion of myocytes to form a multinucleated myotube with contractile capability. In muscle, APC/C^{Cdh1} drives cell differentiation through the destruction of two proteins, Skp2 and Myf5 (Li et al., 2007; **Figure 1**). Elimination of Skp2 leads to the accumulation of the CDK inhibitors p21^{Cip1} and p27^{Kip1} in myoblasts, allowing cell cycle withdrawal. Consistent with a role of p21^{Cip1} in myotube formation, mice lacking p21^{Cip1} fail to form myotubes (Zhang et al., 1999). Thus, the APC/C–Skp2–p21^{Cip1}/p27^{Kip1} axis is likely to be essential for muscle development.

Coupled to APC/C mediated destruction of Skp2 in muscle is APC/C targeting of Myf5. Myf5 is a bHLH transcription factor that regulates myoblast proliferation and homeostasis (Gayraud-Morel et al., 2007). Its expression is restricted to dividing and undifferentiated cells. Myf5 is not directly involved in the decision to differentiate *per se* but in *Myf5* null animals, differentiation is delayed during early regeneration and *Myf5* null mutants are characterized by a subtle progressive myopathy and muscle regeneration deficits (Gayraud-Morel et al., 2007). Degradation of Myf5 by APC/C^{Cdh1} facilitates myogenic fusion, a process required for myoblast differentiation (Gayraud-Morel et al., 2007). Importantly, impaired degradation of both Skp2 and Myf5 seems to have a role in muscle cancer since overexpression of Skp2 and Myf5 are found in cervical carcinoma and rhabdomyosarcomas, respectively (Tamamori-Adachi et al., 2004; Zibat et al., 2010).

Lens cell differentiation

Proper lens differentiation requires precise temporal control of the cell cycle and the coordination of cell cycle exit with differentiation cues and signaling pathways (Zhu and Skoultchi, 2001). APC/C^{Cdh1} has been identified as a crucial regulator of lens differentiation that induces SnoN degradation (Wu et al., 2007). SnoN, a critical transcriptional corepressor of the TGF-β pathway, has been proposed to be a functional switch controlling the expression of p15 and p21^{Cip1} (Zhu et al., 2005). p21^{Cip1} and p15 are two essential cell cycle inhibitors that contribute to cell cycle arrest via downregulation of cyclin D/CDK4/6 activity (Reynisdottir et al., 1995). The upregulation of the p21^{Cip1} and p15 inhibitors is necessary for coupling cell cycle withdrawal in response to TGF-β signaling and the initiation of lens differentiation. Moreover, *Cdh1* depletion was shown to attenuate induction of p15 and p21^{Cip1} and significantly block lens differentiation (Wu et al., 2007). Impaired regulation of SnoN has not been related to corneal tumors but given the importance of APC/C^{Cdh1} in lens differentiation, further studies could open new potential targets in these carcinomas.

Hematopoietic cell differentiation

Hematopoiesis gives rise to all blood cells through a complex series of proliferation and differentiation events that occur throughout lifespan (Kawamoto et al., 2010). The hematopoietic system consists of a large array of differentiated blood cells including erythrocytes and cells of the myeloid and lymphoid lineages. Evidence supporting a role for APC/C^{Cdh1} in hematopoiesis comes from Cdh1 knockout mice. Cdh1 heterozygous mice develop B-cell lymphoma and myelodysplastic disorder (Garcia-Higuera et al., 2008). Although how APC/C^{Cdh1} regulates hematopoiesis remains to be investigated, targeted degradation of Id protein could be one mechanism (**Figure 1**). While Id proteins are downregulated during cell cycle exit, overexpression of Id proteins in terminally differentiated cells triggers cell cycle re-entry. Id proteins modulate cellular proliferation and differentiation in hematopoietic cells (Perk et al., 2005). Id1 is essential for hematopoietic stem cell maintenance and hematopoietic development (Perry et al., 2007) and the balance between Id1 and E-protein regulates myeloid-versus-lymphoid lineage commitment (Cochrane et al., 2009). Dysfunction of *Id2* in mice or cultured cells induces lymphoid differentiation, whereas Id2 overexpression inhibits lymphoid and myeloid differentiation (Perk et al., 2005; Ji et al., 2008). Furthermore, in addition to an Id1 and Id2 requirement for the proliferation and differentiation of hematopoietic precursors, these factors may contribute to the development of myeloid malignancies through enhanced proliferation or inhibited differentiation (Perk et al., 2005).

APC/C^{Cdh1} PRESERVES CHROMOSOME INTEGRITY

Loss of *Cdh1* function produces precocious initiation of DNA synthesis, leading to lower S phase progression, which results in stalled replication forks and under-replicated DNA (Garcia-Higuera et al., 2008). These replicative defects, as well as the upregulation of mitotic kinases, can ultimately lead to genetic damage (Garcia-Higuera et al., 2008; Cotto-Rios et al., 2011). *Cdh1*-deficient cells exhibit defects in mitotic exit and cytokinesis and accumulate a variety of genomic aberrations (Engelbert et al., 2008; Garcia-Higuera et al., 2008). Such genomic aberrations may be a consequence of the inability of APC/C^{Cdh1} to properly mediate a response to DNA damage in *Cdh1* null cells. In G1, APC/C^{Cdh1} targets the ubiquitin specific protease USP1 for proteasome dependent degradation (Cotto-Rios et al., 2011). Since USP1 counteracts monoubiquitination of the DNA repair protein proliferating cell nuclear antigen (PCNA), APC/C^{Cdh1} dependent USP1 destruction allows a permissive environment during G1 for PCNA monoubiquitination, which is required for UV-mediated DNA gap repair (Cotto-Rios et al., 2011). In addition to USP1, APC/C^{Cdh1} controls the levels of multiple proteins involved in the DNA damage checkpoint response and DNA repair including Claspin, Rad17, thymidine kinase 1, and the ribonucleotide reductase subunit (Chabes et al., 2003; Ke et al., 2005; Bassermann et al., 2008; Gao et al., 2009a; Zhang et al., 2010). During G2, the APC/C^{Cdh1} substrate polo-kinase 1 (Plk1) controls CDK1 activation and recovery from DNA replication stresses (Watanabe et al.,

2004; Mamely et al., 2006). Cells exposed to genotoxic stress in G2 need to arrest the cell cycle and repair damaged DNA. One mechanism to achieve this is to reduce levels of proteins such as Plk1 and mitotic cyclins, which are required for mitotic entry. Although normally inactive during G2, APC/C^{Cdh1} is activated via Cdh1 dephosphorylation during genotoxic stress, which is mediated by the Cdc14B phosphatase (Bassermann et al., 2008). Therefore, participation of APC/C^{Cdh1} in the G2 DNA damage response suggests another mechanism for genomic instability observed in *Cdh1* null cells.

APC/C^{Cdh1} MODULATORS AS TUMOR SUPPRESSOR PROTEINS OR ONCOGENES

Considering the prominent role of APC/C in cell cycle regulation and genomic stability, it is tempting to speculate that its dysregulation triggers a major perturbation of cell cycle progression and contributes to cell transformation. In fact, hemizygous frameshift and point mutations in several subunits of APC/C have been found in colon cancer cell lines and tumors (Wang et al., 2003). Mutations in *Apc3*, *Apc6*, and *Apc8* were found in colon cancer, breast cancer, neuroblastoma, hepatocarcinoma, melanoma, glioma, choriocarcinoma, endometrial cancer, ovarian cancer, and prostate carcinoma (Wang et al., 2003). Overexpression studies of Apc8 suggested that APC/C mutations can act in a dominant-negative manner to inhibit its function and cause inappropriate cell cycle progression (Wang et al., 2003). Moreover, the APC/C cofactor *Cdh1* has been described as a *tumor* suppressor (Garcia-Higuera et al., 2008). Knockdown or inhibition of *Cdh1* is associated with centrosome amplification and chromosome mis-segregation, and is implicated in genomic instability and tumorigenesis (Ross and Cohen-Fix, 2003; Wasch and Engelbert, 2005; Engelbert et al., 2008; Garcia-Higuera et al., 2008). *Cdh1*-deficient mice display genomic instability and heterozygous *Cdh1* mice develop epithelial tumors, such as mammary gland adenocarcinomas and fibroadenomas, which are not observed in wild-type mice. Furthermore, these tumors contain one *Cdh1* wild-type allele, suggesting that *Cdh1* is haploinsufficient for tumor suppression. In addition to mutations in APC/C or Cdh1 subunits, it is tempting to speculate that alterations of APC/C upstream regulators may lead to transformation (**Table 1**).

RETINOBLASTOMA PROTEIN

A well-established tumor suppressor protein that positively regulates APC/C activity is the pRB. pRB plays multiple roles during the cell cycle; it blocks cell cycle progression from G1 to S phase, and guards the cell from replicating damaged DNA, thus preventing the integration of mutations into the genome. This tumor suppressor function requires binding and repressing the E2F family transcription factors (Classon and Harlow, 2002; Chen et al., 2009). Reversion of the pRb–E2F interaction occurs after mitogenic stimuli sufficient for the activation of CDKs that phosphorylate pRB in the nucleus. Subsequently, phospho-pRb is released from E2Fs, which can then induce S phase entry (Thoma et al., 2011). Consistent with a direct inhibitory role in S phase entry, loss of various pRBs leads to unscheduled cell proliferation in many tissues (Vidal and Koff, 2000; Cobrinik, 2005; Marx et al., 2010). Accordingly, mutations in *Rb* are found in a wide variety of cancers mainly

in the lung, breast, and eye (Meraldi et al., 1999; Sabado Alvarez, 2008).

Retinoblastoma protein also possesses E2F-independent functions that contribute to cell cycle control. pRB interacts with both Skp2 (Ji et al., 2004) and with APC/C^{Cdh1} through distinct surfaces (Binné et al., 2007). pRB needs to interact with both proteins to target Skp2 for ubiquitin-mediated degradation and promote p27^{Kip1} accumulation and cell cycle exit. Interestingly, similar to E2F1, Cdh1 only interacts with the hypophosphorylated (active) form of pRb, and phosphorylation of pRb by cyclin A/CDK2 kinase abolished the ability of Rb to interact with both Cdh1 and E2F1. Therefore Cdh1, by competing with pRb interaction, can also regulate the activity of the E2F1 transcription factor (Sorensen et al., 2000; Gao et al., 2009a). Further, given that both pRB and Cdh1 have tumor suppressive functions, whether the pRB–APC/C^{Cdh1} interaction is misregulated during tumorigenesis should be investigated (**Figure 2**).
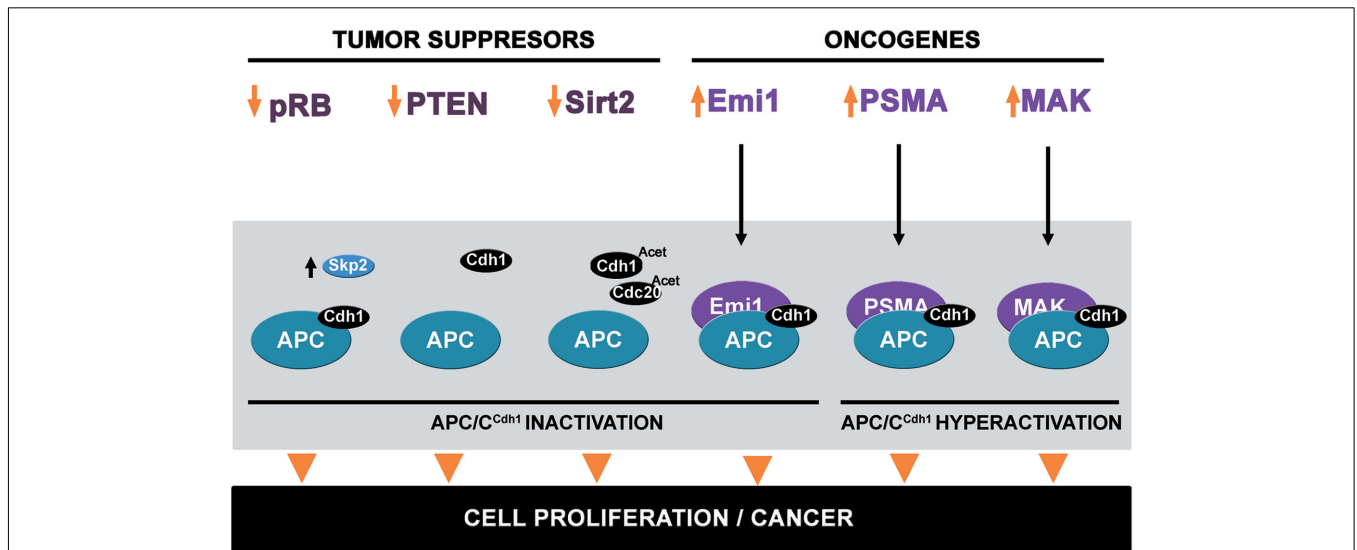
PTEN

Recent studies have demonstrated that the well-characterized tumor suppressor protein PTEN is a positive regulator of APC/C activity. PTEN (Cairns et al., 1997; Steck et al., 1997; Feilotter et al., 1998; Gray et al., 1998; Li and Sun, 1998) encodes a lipid phosphatase, which plays a crucial role in adhesion, migration, growth, and apoptosis. *Pten*-null mice die embryonically, but heterozygous mice survive and develop tumors in the lymphoid system, endometrium, prostate, and the thyroid (Di Cristofano et al., 1998; Podsypanina et al., 1999). *Pten* somatic mutations occur in a large percentage of human cancers, with the highest numbers found in endometrial, central nervous system, skin, and prostate cancers (Chalhoub and Baker, 2009).

The effects observed after PTEN loss have been attributed to activation of the PI3K/AKT pathway as PTEN can dephosphorylate phosphoinositide-3,4,5-triphosphate (PIP3), a potent activator of Akt1 (Maehama and Dixon, 1998). PTEN inactivation by phosphorylation or oxidation in human cancer results in elevated Akt1 activity and abnormal growth regulation (Silva et al., 2008; Chalhoub and Baker, 2009; McCubrey et al., 2011). However, functions independent of its phosphatase activity have been described (Maier et al., 1999; Georgescu et al., 2000; Koul et al., 2002a,b; Gildea et al., 2004; Blanco-Aparicio et al., 2007). Recently, a novel interaction between PTEN and APC/C^{Cdh1} has been reported (Song et al., 2011). Song et al. (2011) demonstrated that nuclear PTEN directly enhances the activity of APC/C by promoting its association with Cdh1 in a phosphatase-independent manner. Conversely, PTEN loss impairs the activity of the APC/C^{Cdh1} complex. Therefore, loss of PTEN function decreases APC/C^{Cdh1} activity, suggesting novel molecular pathways that may be involved in the progression and initiation of tumorigenesis. This in turn highlights the complexity of the dose-dependent tumor promoting and fail-safe cellular responses evoked by PTEN loss. Accordingly, tumor-derived mutations that do not affect the phosphatase enzymatic activity of PTEN *in vitro* have also been identified. These were found to affect the compartmentalization of PTEN in the cell, either by sequestering PTEN in the nucleus (Denning et al., 2007) or by interfering with PTEN's recruitment to the plasma membrane (Lee et al., 1999; Georgescu et al., 2000; Walker et al.,

Table 1 | Modulators of APC/C^{Cdh1} dysregulated in cancer.

APC/C regulator	Effects on APC/C	Major cell cycle function (s)	Role in tumorigenesis	Relevant cancers	Relevant reference
PTEN	Activator. Promotes the interaction between APC/C and Cdh1	Promotes cell differentiation. Downregulation promotes cell proliferation	Acts as a tumor suppressor. Null mice die and heterozygous develop tumors	Lymphoid system, endometrium, thyroids, central nervous system, skin, prostate, breast	Chalhoub et al. (2009), Hollander et al. (2011), Song et al. (2011), Uddin et al. (2004), Kwon et al. (2008)
pRB	Activator. Promotes degradation of Skp2 by interaction with APC/C and Skp2	Blocks progression of G1/S. Downregulation promotes cell proliferation	Acts as a tumor suppressor. Prevents integration of DNA damage	Lung, breast, eye	Chen et al. (2009), Classon and Harlow (2002), Ji et al. (2004), Binné et al. (2007), Sabado Alvarez (2008)
Sirt2	Activator. Acetylates Cdh1 and Cdc20 promoting their interaction with APC/C	Regulates chromosomal condensation during mitosis. Maintains genome integrity	Acts as a tumor suppressor. Decrease of function promotes genome instability	Breast, liver, brain, kidney, and prostate cancers	North and Verdin (2007), Kim et al. (2011)
PSMA	Activator. Associates with Cdc27	Unknown	Acts as an oncogene. Overexpression promotes premature activation of APC/C and aneuploidy	Prostate cancer	Rajasekaran et al. (2005, 2008), Burger et al. (2002), Chang et al. (1999, 2001)
Emi1	Inhibitor. Binds to APC/C	Permits accumulation of cyclins in G1/S	Overexpression with p53 knock down promotes proliferation and chromosomal instability	Kidney, liver, lung, endometrium, lymphoid system, ovarium, lung	Hsu et al. (2002), Miller et al. (2006), Lehman et al. (2006), Gütgemann et al. (2008)
MAK	Inhibitor. Phosphorylates Cdh1	Promotes stabilization of APC/C^{Cdh1} substrates	Acts as an oncogene. Overexpression promotes extra-centrosomes	Prostate cancer	Wang and Kung (2011)

FIGURE 2 | Dysregulation of APC/C^{Cdh1} modulators can promote cancer. Decreasing expression of the tumor suppressors pRB, PTEN, and Sirt2 may promote APC/C^{Cdh1} inactivation, leading to cell proliferation and tumorigenesis. pRB downregulation may decrease Skp2 destruction. Decreasing PTEN levels might reduce APC/C activity. Decrease of Sirt2 could enhance the acetylation of the coactivators Cdh1 and Cdc20, lowering the capacity to interact with APC/C. In addition to the tumor suppressors, the oncogenes Emi1, PSMA, and MAK also regulate APC/C^{Cdh1} activity. Emi1 binds as a pseudo-substrate and leads to APC/C inactivation. PSMA and MAK increase APC/C^{Cdh1} activity and produce genomic instability.

2004), thus possibly negatively impacting the PTEN–APC/C^{Cdh1} interaction. Consistent with this possibility, APC/C^{Cdh1} substrates are overexpressed in tumors containing PTEN deficiency (Marino et al., 2002; Gao et al., 2009a; Liu et al., 2011b). Further, PTEN over-expression has been found to suppress tumorigenesis by inducing G1 cell cycle arrest in human glioblastoma cells (Li and Sun, 1998). Given the importance of PTEN and APC/C^{Cdh1} for cancer pro-gression, it will be crucial to determine whether tumors containing PTEN misregulation have both hyeractivation of the Akt1 pathway and dysregulation of APC/C^{Cdh1} function (**Figure 2**).

EARLY MITOTIC INHIBITOR-1

The Emi1 is an APC/C inhibitor, which is overexpressed in mul-tiple tumors. Emi1 is a key cell cycle regulator that is required for accumulation of mitotic cyclins and other critical cell cycle regulators during S phase and G2 (Hsu et al., 2002). At the G1/S transition, Emi1 functions as a pseudo-substrate inhibitor of the APC/C (Miller et al., 2006), allowing substrates to accumulate (Guardavaccaro et al., 2003; Miller et al., 2006). In early mito-sis, Emi1 is phosphorylated by Plk1 (Hansen et al., 2004), which triggers SCF$^{\beta TrCP}$-dependent ubiquitination and destruction, thus inducing APC/C activation and mitotic progression (Margottin-Goguet et al., 2003). Emi1 overexpression leads to unscheduled cell proliferation, tetraploidy, and chromosomal instability in *p53*-deficient cells (Lehman et al., 2006; **Figure 2**). In *p53* wild-type cells, the induction of tetraploidy and aneuploidy by overex-pressing APC/C inhibitors like Emi1 typically leads to G1 arrest or apoptosis. Indeed, Emi1 overexpression causes mitotic cata-strophe and genomic instability through APC/C misregulation, and thus potentially contributes to tumorigenesis (Hsu et al., 2002). Upregulation of *Emi1* mRNA has been found in a variety of malignant tumors compared to matched normal and benign tumor tissue. Notably, Emi1 protein is highly expressed in renal cell carcinomas, cervical adenocarcinomas, hepatocellular car-cinomas, oligodendrogliomas, lung adenocarcinomas, endome-trial cancers, of melanomas, many lymphomas and ovarian clear cell carcinoma (Lehman et al., 2006; Gütgemann et al., 2008). Emi1 expression is also related to the pRB/E2F pathway since Emi1 is a target of the E2F transcription factor. At the G1-S transition Emi1 is transcriptionally induced by E2F, thus accel-erating S phase entry (Hsu et al., 2002). The importance of this regulation is underscored by the finding that lack of pRb repression of E2F-mediated transcription causes misregulation of Emi1 and APC/C substrates in malignant tumors (Lehman et al., 2006).

Sirt2

Recently, the histone deacetylase (HDAC) SIRT2 has been shown to positively regulate APC/C activity (Kim et al., 2011). Histone acetyltransferases (HATs) and HDACs are enzymes controlling protein acetylation. Both target histones, whereas HATs catalyze the acetylation of histones and relax chromatin to increase acces-sibility of transcription factors to promoters of target genes, HDACs remove acetyl groups from histones and repress transcrip-tion (Strahl and Allis, 2000). Most of them have been found in transcription factor complexes and, therefore, have been consid-ered to regulate transcription by modulating acetylation levels of

chromatin (Kuo and Allis, 1998; Kouzarides, 1999). HDACs are important for cell cycle progression and their inhibition promote cell arrest in G1 and G2 (Marks et al., 2001; Johnstone and Licht, 2003; Noh and Lee, 2003). HDACs also have an important role in heterochromatin formation and maintenance (Olsson et al., 1999; Taddei et al., 2001) and are implicated in chromosome segregation (Nakayama et al., 2003; Silverstein et al., 2003; Kimata et al., 2008).

Several HDACs have a role in tumorigenesis, acting as a sup-pressors or promoters (Lagger et al., 2002; Glaser et al., 2003; Saunders and Verdin, 2007; Wang et al., 2008a,b; Deng, 2009; Bell et al., 2011; Kim et al., 2011) and HDAC inhibitors are a promis-ing class of anti-cancer agents (Johnstone and Licht, 2003; Yoshida et al., 2003; Bolden et al., 2006). SIRT2 is predominantly localized in the cytoplasm where it deacetylates microtubules (North et al., 2003). During mitosis, SIRT2 is localized to chromosomes reg-ulating chromosomal condensation (Vaquero et al., 2006; Inoue et al., 2007), and is also associated with mitotic structures, includ-ing the centrosome, mitotic spindle, and midbody, presumably to ensure normal cell division (North and Verdin, 2007). Kim et al. (2011) demonstrated that SIRT2 regulates APC/C activ-ity through deacetylation of its coactivators Cdh1 and Cdc20. Deacetylation of Cdh1 and Cdc20 by SIRT2 enhances the inter-action of these coactivators with Cdc27, leading to activation of APC/C. In *Sirt2* mutant mice, reduced APC/C activity results in tumor formation by producing genomic instability associ-ated with centrosome amplification, aneuploidy mitotic cell death, and spontaneous tumor formation. These deficiencies seem to be caused by a combined effect of altered expression of mitotic regu-lators that are controlled by APC/C (**Figure 2**). Accordingly, SIRT2 expression is reduced in several human malignancies includ-ing breast, liver, brain, kidney, and prostate cancers (Kim et al., 2011).

PSMA AND MAK

Mitotic defects associated with chromosomal aberrations are often observed in prostate cancer cells and tissue, suggesting possible misregulation by APC/C (Tribukait, 1991; Beheshti et al., 2001; Pihan et al., 2001). Two regulators of the APC/C have been found to be clearly involved in prostate cancer, prostate spe-cific membrane antigen (PMSA) and male germ cell-associated kinase (MAK). PSMA is a type II transmembrane protein that exhibits both *N*-acetylated alpha-linked acidic peptidase (NAAL-ADase) and folate hydrolase activities (Ghosh and Heston, 2004; Rajasekaran et al., 2005). PSMA is localized to secretory cells within the prostatic epithelium although its physiological and pathological functions remain unclear. PSMA is upregulated in advanced prostate carcinoma and metastatic disease (Rajasekaran et al., 2005), and is a feature of practically every prostatic tissue examined (Rajasekaran et al., 2005, 2008). PSMA is absent or mod-erately expressed in hyperplastic and benign tissues, while malig-nant tissues have high levels, demonstrating that PSMA expression increases proportionally to tumor aggressiveness (Troyer et al., 1995; Kawakami and Nakayama, 1997; Liu et al., 1997; Silver et al., 1997; Sweat et al., 1998; Chang et al., 1999, 2001; Burger et al., 2002; Ross et al., 2003). PSMA is localized to a mem-brane compartment in the vicinity of centrosomes at the spindle poles and associates with the APC/C subunit Cdc27 leading to

premature activation of APC/C, and induction of aneuploidy (Rajasekaran et al., 2008). Increased APC/C activity observed in PSMA expressing cells is sufficient to impair the mitotic spindle checkpoint, which agrees with the finding that PSMA expressing cells exit mitosis prematurely (**Figure 2**). Therefore, PSMA may have a causal role in the progression of prostate cancer.

Male germ cell-associated kinase belongs to a protein kinase family characterized by a catalytic domain resembling a hybrid of the TXY motif found in mitogen-activated protein kinases (MAPK) and the TY motif in CDKs (Payne et al., 1991; Brown et al., 1999; Xia et al., 2002; Fu et al., 2005). MAK expression is elevated in castration-resistant prostate cancer cell lines and is generally overexpressed in prostate tumors, thus possibly contributing to malignancy via aberrant regulation of mitosis (Wang and Kung, 2011). MAK protein has a dynamic subcellular localization during the cell cycle: it is localized to the mitotic spindle and centrosomes during metaphase and anaphase, and to the mitotic midbody from anaphase to telophase. MAK negatively regulates APC/C^{Cdh1} through interaction and phosphorylation of Cdh1 in CDK phosphorylated sites, in a manner reminiscent of CDK-dependent inactivation of Cdh1 (Wang and Kung, 2011; **Figure 2**). The phosphorylation of MAK increases between S and G2, peaks at early mitosis, and drastically decreases at the end of mitosis. This promotes the dissociation of Cdh1 and APC/C thus decreasing APC/C^{Cdh1} activity and promoting the stabilization of the substrates Aurora kinase A and Plk1. As overexpression of Aurora-A is known to induce centrosome amplification (Zhou et al., 1998), the extra-centrosomes observed in MAK overexpressed cells is likely due to cellular accumulation of Aurora-A.

APC/C SUBSTRATES IN CANCER

Many APC/C substrates have been implicated in a variety of human cancers (**Table 2**). For those substrates that are overexpressed in cancer it is important to note that overexpression of an APC/C substrate influences degradation of other APC/C substrates (Rape and Kirschner, 2004), suggesting that global estimates of APC/C substrate levels are required in normal and disease states. Further, while there are arguably many APC/C substrates that may be important for cancer progression, classifying their relative importance and druggability is essential.

NIMA-RELATED KINASE 2

The proteolysis of APC/C substrates starts as cells make the transition from G2 to M phase. One of the earliest targets is the NIMA-related kinase 2 (Nek2) family of serine/threonine protein kinases. They are implicated in the regulation of centrosome separation and spindle formation. Nek2A, along with cyclin A are unique APC/C^{Cdc20} substrates that get degraded during prometaphase even when the SAC is active. A C-terminal dipeptide methionine–arginine (MR) tail enables Nek2A to directly bind the APC/C independently of Cdc20 (Hayes et al., 2006). Nek2 levels are upregulated in human breast cancer, pediatric osteosarcoma, and B-cell lymphomas (Wai et al., 2002; de Vos et al., 2003; Hayward et al., 2004).

CELL DIVISION CYCLE PROTEIN 20

Cell division cycle protein 20 is an essential coactivator of the APC/C during mitosis. Multiple studies have indicated that maintaining appropriate Cdc20 levels is important for cellular homeostasis. When this is disturbed and Cdc20 is overexpressed, tumorigenesis can occur. For instance, oral squamous cell carcinomas (OSCC) and breast cancer cells overexpress Cdc20 causing premature anaphase and aneuploidy linked to tumor formation (Yuan et al., 2006; Mondal et al., 2007). Importantly, even a twofold overexpression of Cdc20 leads to spindle checkpoint defects and early Pds1 (securin) destruction producing aneuploidy (Pan and Chen, 2004).

One of the major ways Cdc20 protein levels are controlled is via the SAC. When the SAC is active during metaphase, the checkpoint proteins Mad2, BubR1, and Bub3 bind to Cdc20 and convert it into a substrate of APC/C^{Cdc20}. This allows for the ubiquitination and degradation of Cdc20 by APC/C^{Cdc20} (Nilsson et al., 2008; Ge et al., 2009). Thus, SAC activation inhibits Cdc20 and arrests cells in metaphase. Inactivation of SAC at the end of metaphase relieves this inhibition and Cdc20 promotes mitotic exit by degrading key substrates such as the mitotic cyclins. The importance of SAC dependent control of Cdc20 levels is underscored by the finding that anti-mitotic cancer drugs that activate the SAC cause cell cycle arrest. These drugs cause a prolonged metaphase arrest that may eventually lead to cell death. However, during this prolonged metaphase arrest, some Cdc20 escapes inhibition by the SAC and as a result, cyclin B1 levels start to fall and cells exit mitosis, thereby initiating mitotic slippage (Nilsson, 2011). This may be especially true in some cancer subtypes since the frequency of mitotic slippage is hastened in tumor cells lacking p53 and pRb (Depamphilis, 2011). Further, mitotic slippage reduces the sensitivity of tumor cells to chemotherapeutics. Thus, alternative means of inhibiting Cdc20 are needed.

Recent evidence suggests that targeting Cdc20 directly could be a better alternative than targeting the SAC in cancer therapy (Huang et al., 2009; Manchado et al., 2010). Knockdown of Cdc20 by siRNA induces mitotic arrest and apoptosis in various cancer cell lines that are otherwise resistant to apoptosis and prone to mitotic slippage (Huang et al., 2009). Further, genetic ablation of the *Cdc20* gene in murine skin tumor and aggressive fibrosarcoma models results in complete tumor regression (Manchado et al., 2010). *Cdc20* deletion induces metaphase arrest and apoptosis in tumor cells both *in vitro* and *in vivo*. Importantly, the activities of Cdk1 and Mast1 kinases are required for this arrest. When Cdk1 and Mast1 kinases are inhibited, *Cdc20* null cells exit mitosis via the activities of the phosphatases PP2A/B55α and PP2A/B55δ (Manchado et al., 2010). Thus, small molecules attenuating Cdc20 coupled with those inhibiting these phosphatases may be effective therapeutically.

GEMININ

Another APC/C substrate degraded at the metaphase–anaphase transition is geminin. It is a small 25 kDa protein that inhibits DNA re-replication during S phase. Geminin levels accumulate during S, G2, and early mitosis. It suppresses the DNA replication factor CDT1 that is required for the formation of preRCs. Depletion of geminin by siRNA in tumor cells leads to DNA re-replication, cell

cycle arrest, and apoptosis. However, regulation of CDT1 by geminin is found to be rate limiting for initiation of DNA replication only in cancer cells and not in normal or immortalized cells. Normal cells show the same effect only when cyclin A is co-depleted with geminin (Zhu and Depamphilis, 2009). Thus it has been proposed that inhibition of geminin activity can be used to selectively kill cancer cells (Zhu and Depamphilis, 2009).

POLO-LIKE KINASE 1

Toward the end of anaphase, the pro-mitotic regulatory kinase Plk1, is degraded by APC/C^{Cdh1} in a D-box dependent manner (Lindon and Pines, 2004). Plk1 is a major kinase in eukaryotic cells involved in a variety of processes such as activation of the maturation promoting factor (MPF) by phosphorylation of Cdc25C and cyclin B1, bipolar spindle formation, and maturation of the centrosome (Ohkura et al., 1995; Lane and Nigg, 1996; Abrieu et al., 1998; Qian et al., 1998; Eckerdt et al., 2005). Elevated Plk1 levels are present in a broad spectrum of cancers including breast cancer, colorectal cancer, ovarian cancer, melanomas, pancreatic cancer, prostate cancer, lung cancer, and squamous cell carcinomas of the head and neck (Wolf et al., 1997, 2000; Knecht et al., 1999; Strebhardt et al., 2000; Macmillan et al., 2001; Gray et al., 2004; Weichert et al., 2004). This broad range of expression makes Plk1 a prime target in cancer (Strebhardt and Ullrich, 2006).

AURORA-A

Another APC/C^{Cdh1} substrate during late mitosis is Aurora-A (STK15/BTAK), a serine/threonine kinase localized to the centrosome controlling mitotic spindle assembly and centrosome maturation. It is involved in a variety of human cancers (Bischoff et al., 1998; Zhou et al., 1998; Sen et al., 2002; Mondal et al., 2007). Ectopic expression of Aurora-A leads to chromosome instability and centrosome amplification (Miyoshi et al., 2001). One way it achieves this is by phosphorylating and regulating Centrin, the calcium-binding phosphoprotein located in the centrosome. Phosphorylated Centrin is more stable against APC/C^{Cdh1} mediated destruction and an excess of it is thought to promote centrosome amplification in cancer (Lukasiewicz et al., 2011). Aurora-A itself becomes resistant to APC/C^{Cdh1} mediated degradation when it is constitutively phosphorylated on Ser 51, and consequently gets overexpressed in head and neck cancers (Kitajima et al., 2007).

HIGH EXPRESSION IN CANCER 1

High expression in cancer 1 (HEC1), a recently identified APC/C^{Cdh1} substrate, is part of the NDC80 complex controlling kinetochore microtubule dynamics. HEC1 levels peak during early mitosis and fall by telophase (Lipkowitz and Weissman, 2011). The mitotic regulatory kinase Nek2 phosphorylates HEC1 on Ser 165 thus activating it during G2/M. Inactivation of HEC1 results in severe chromosome segregation defects (Chen et al., 1997, 2002; Zheng et al., 1999). HEC1 is considered as a candidate marker for breast lesions likely to undergo malignant transformation because it is significantly overexpressed in benign breast tumors (Bieche et al., 2011). A small molecule called INH1, which binds to HEC1 and specifically disrupts the HEC1–Nek2 interaction, is found to suppress human breast cancer cell proliferation in culture as well as tumor growth in nude mice bearing xenografts (Wu et al., 2008).

c-Jun NH2-TERMINAL KINASE

c-Jun NH$_2$-terminal kinase (JNKs), a class of MAPK, lead the cell's response to stress stimuli such as heat shock, radiation, and cytotoxic and genotoxic stress. Recently, nuclear JNK was found to be a substrate of APC/C^{Cdh1} during late mitosis and G1 (Gutierrez et al., 2010a). JNK, in turn, controls APC/C^{Cdh1} by phosphorylating Cdh1 at three residues (Yu et al., 1998; Summers et al., 2008) to prevent premature Cdh1 association with the APC/C during G2. JNK-induced phosphorylation of key regulators not only controls cell survival and differentiation, but also cell cycle progression. JNK phosphorylates Cdc25C at Ser 168 in G2, downregulating its phosphatase activity required for CDK1 activation (Gutierrez et al., 2010b). This is required for the correct timing of mitotic entry and the proper establishment of G2/M checkpoint upon UV irradiation. However, constitutively active JNK causes defects in cell cycle progression. Indeed, many human tumors have been reported to require JNK activity for their growth and survival (Potapova et al., 2000; Antonyak et al., 2002; Tsuiki et al., 2003; Yang et al., 2003; Lopez-Bergami et al., 2007; Alexaki et al., 2008). In gastrointestinal cancers, a small molecule inhibitor of JNK shows promise as a therapeutic agent, because it induces cell cycle arrest and apoptosis (Xia et al., 2006).

Ect2

The oncogenic protein Ect2 is ubiquitinated by APC/C^{Cdh1} shortly after completion of mitosis (Liot et al., 2011). Ect2 is a positive regulator of the Rho GTPase pathway that controls cell cycle progression and cytokinesis (Bustelo et al., 2007). Many human tumors overexpress Ect2 (Sano et al., 2006; Salhia et al., 2008; Justilien and Fields, 2009; Justilien et al., 2011). Until now, this overexpression was believed to be a result of gene amplification and transcriptional upregulation (Seguin et al., 2009; Liot et al., 2011). But the newly discovered APC/C^{Cdh1} dependent proteolysis of Ect2 shows that impaired destruction can also be a reason for increased Ect2 levels in tumor cells, which possibly asserts the role of Cdh1 as a tumor suppressor protein.

Skp2

Skp2 is one of the most important substrates targeted by APC/C^{Cdh1} during mitotic exit. An SCF containing Skp2 targets the essential cell cycle substrates p27^{Kip1}, p21^{Cip1}, and FOXO1 for degradation (Yu et al., 1998; Tsvetkov et al., 1999; Huang et al., 2005). Destruction of the CDK inhibitor p27^{Kip1} is a prerequisite for entry into mitosis. Once cells exit mitosis, APC/C^{Cdh1} targets Skp2 for proteolysis in G1 (Bashir et al., 2004; Wei et al., 2004). Skp2 functions as an oncogene because most of its ubiquitination targets are tumor suppressor proteins. Thus overexpression of Skp2 is common in many cancers including breast cancer, prostate cancer, pancreatic cancer, hepatocellular carcinomas, melanomas, and malignant lymphomas (Lim et al., 2002; Yang et al., 2002; Radke et al., 2005; Lu et al., 2009; Rose et al., 2011; Schuler et al., 2011). Importantly, the Akt1 serine/threonine kinase phosphorylates Skp2 at Ser 72 promoting its cytoplasmic translocation and impairing degradation by APC/C^{Cdh1} (Gao et al., 2009b,c; Lin et al., 2009). Since the Akt1 pathway is also found to be hyperactive in cancer cells, it may contribute significantly to overexpression of Skp2 protein found in some cancers (Gao et al.,

2009b,c). Opposing the Akt1 pathway is PTEN, which is frequently misregulated in human brain, breast, prostate cancers, and leukemias (Li et al., 1997; Dahia et al., 1999). Thus, PTEN misregulation may contribute to Akt1 hyperactivation and increased levels of Skp2 in tumors.

Ube2C (UbcH10)

Ube2C is an E2 enzyme that works exclusively with the APC/C throughout the cell cycle. However, Ube2C levels peak during mitosis and fall as cells enter G1, finally becoming a substrate for APC/C^{Cdh1} at the end of G1 (Rape and Kirschner, 2004; Summers et al., 2008). When Ube2C is overexpressed in mouse embryonic fibroblasts (MEFs), precocious cyclin B1 degradation, mitotic slippage, and chromosome abnormalities have been observed (van

Ree et al., 2010). Importantly, elevated Ube2C levels is a common feature in a wide variety of human cancers including lung, prostate, breast, bladder, ovarian, uterine, thyroid, esophageal, and gastric carcinomas (Okamoto et al., 2003; Pallante et al., 2005; Berlingieri et al., 2007; Jiang et al., 2008; van Ree et al., 2010). Further, induced expression of high levels of Ube2C hastens tumor formation in transgenic mice (van Ree et al., 2010).

MODULATING APC/C^{Cdh1} ACTIVITY IN CANCER
TARGETING APC/C^{Cdh1} SUBSTRATES

Several APC/C substrates are overexpressed in various cancers, making them prime targets for small molecule inhibition (**Table 2**). One potential APC/C substrate that could be targeted

Table 2 | Substrates of APC/C overexpressed in cancer.

APC/C substrate	Major cell cycle function(s)	Role in tumorigenesis	Relevant cancers	Relevant reference
Nek2	Regulation of centrosome separation and spindle formation	Formation of multinucleated cells with supernumerary centrosomes	Cervical cancer, B-cell lymphoma, pediatric osteosarcoma, breast cancer, leukemia, ovarian cancer	Wai et al. (2002), de Vos et al. (2003), Hayward et al. (2004)
Cdc20	Essential APC/C coactivator in early mitosis	Spindle checkpoint defects and premature Securin destruction leading to mitotic slippage	Oral squamous cell carcinomas, breast cancer	Yuan et al. (2006), Mondal et al. (2007)
Plk1	Activation of MPF by phosphorylation of Cdc25C and Cyclin B Assembling the mitotic spindle	Overexpression in cancer drives cells into mitosis	Lung, ovarian, breast, colon, prostate and pancreatic cancers, head/neck squamous cell carcinomas, melanomas	Wolf et al. (1997), Knecht et al. (1999), Strebhardt et al. (2000), Wolf et al. (2000), Macmillan et al. (2001), Gray et al. (2004), Weichert et al. (2004)
Aurora-A	Controls centrosome maturation and mitotic spindle formation	Induces centrosome amplification and aneuploidy by hindering APC/C^{Cdh1} mediated destruction of Centrin	Bladder, lung, and colon cancers	Bischoff et al. (1998), Zhou et al. (1998), Sen et al. (2002), Gu et al. (2007)
HEC1	Controls kinetochore microtubule dynamics as part of the NDC80 complex	Chromosome mis-segregation	Breast cancer	Bieche et al. (2011)
JNK	Central role in stress response pathways Ensures correct timing of mitotic entry by phosphorylating Cdc25C	Supports survival of tumor cells by controlling cell cycle arrest and apoptosis	Brain tumors such as glioblastoma, prostate cancer, gastrointestinal cancers, melanomas	Potapova et al. (2000), Antonyak et al. (2002), Tsuiki et al. (2003), Yang et al. (2003), Xia et al. (2006), Lopez-Bergami et al. (2007), Alexaki et al. (2008)
Ect2	Positive regulator of the Rho GTPase pathway that controls actin cytoskeleton functions like cytokinesis	Ensures proper cytokinesis in tumor cells	Glioblastoma, non-small cell lung cancer	Salhia et al. (2008), Justilien et al. (2011)
Skp2	F-box protein that functions as part of SCF^{Skp2} to degrade Cdk inhibitors p27^{Kip1} and p21^{Cip1}	Acts as an oncogene that destroys tumor suppressor proteins	Breast, prostate, liver and pancreatic cancers, melanomas, lymphomas	Lim et al. (2002), Radke et al. (2005), Lu et al. (2009), Rose et al. (2011), Schuler et al. (2011)
Ube2C (UbcH10)	Principal E2 enzyme the APC/C collaborates with	Chromosome abnormalities and mitotic slippage	Gastric carcinomas, cancers of the lung, prostate, breast, ovary, bladder, thyroid, uterus, and esophagus	Okamoto et al. (2003), Pallante et al. (2005), Berlingieri et al. (2007), Jiang et al. (2008), van Ree et al. (2010)

via such a strategy is the proto-oncogene Skp2 (Fujita et al., 2008, 2009). Downregulation of Skp2 by antisense RNA treatment induces apoptosis in lung cancer cells (Yokoi et al., 2003). Therefore, one possibility is utilizing compounds affecting Skp2 expression. For instance, treatment with EB1089 (vitamin D analog) reduces Skp2 expression in treated cancer cells, thus promoting increased stability of p27^{Kip1} protein and subsequent growth arrest (Lin et al., 2003; **Figure 3**). Skp2 expression is also affected by treatment with retinoic acid, thus altering the ability of p27^{Kip1} to be ubiquitinated (Nakamura et al., 2003). Furthermore, the PPARg agonist Troglitazone reduces *Skp2* mRNA levels, leading to p27^{Kip1} accumulation (Koga et al., 2003).

Since the APC/C mediates Skp2 ubiquitination, enhancing APC/C dependent degradation of Skp2 in cancer would also be therapeutically attractive. One possible means of achieving this is to inhibit casein kinase 1 (CK1), which controls APC/C dependent degradation of Skp2 (Gao et al., 2009b,c). CK1 inhibition induces Skp2 degradation since CK1 dependent phosphorylation normally inhibits Skp2 nuclear translocation and interaction with APC/C^{Cdh1} (Gao et al., 2009b,c). An alternative strategy, however, could be increasing the affinity of Skp2 or other oncogenic substrates for APC/C, thus reducing their protein levels after ubiquitination and degradation. The advent of high-throughput screens to study APC/C-dependent degradation and protein–protein interactions will facilitate identification of small molecule agonists of the APC/C–Skp2 interaction (Madoux et al., 2010; Zeng et al., 2010).

Another potential APC/C cancer target is the substrate Aurora-A, since its overexpression is known to induce centrosome amplification and is overexpressed in human cancer cells (Zhou et al., 1998). Recently, several compounds have been found to target Aurora-A (**Figure 3**). Curcumin, an active compound in turmeric and curry that has been proven to induce tumor apoptosis and inhibit tumor proliferation, invasion, angiogenesis, and metastasis, has been shown to reduce *Aurora-A* mRNA expression in human bladder cancer cells (Liu et al., 2011a). These curcumin-induced phenomena were similar to those using Aurora-A small interfering RNA and were attenuated by ectopic expression of
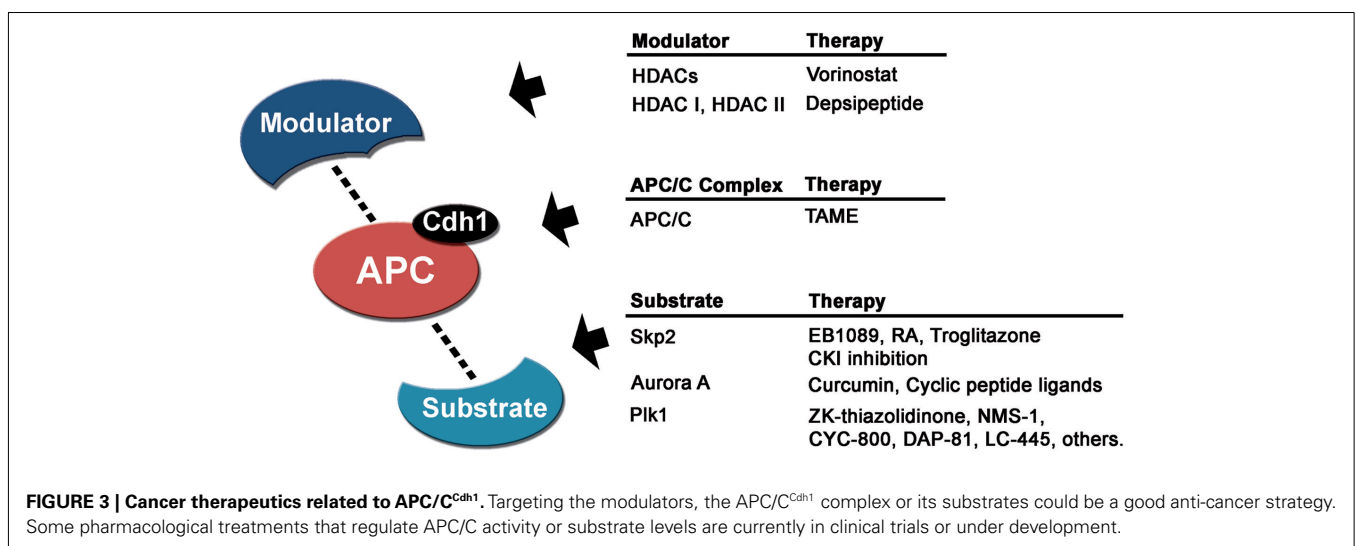
Aurora-A. Also, several cyclic peptide ligands inhibiting Aurora-A kinase activity have been developed (Shomin et al., 2011), although future studies regarding proliferation of cancer cells still have to be performed.

In addition to Aurora-A inhibition, there is pharmaceutical interest in targeting Plk1 as Plk1 depletion in cancer cells dramatically inhibits cell proliferation and decreases viability (Liu and Erikson, 2003; Xu et al., 2011; Yoon et al., 2011). Depletion of Plk1 perturbs spindle assembly, which leads to activation of the mitotic checkpoint, prolonged mitotic arrest, and eventually apoptosis (Liu and Erikson, 2003). Thus, given the known functions and effects of Plk1 inhibition, coupled with its wide overexpression pattern in cancer, a naturally occurring Plk1 inhibitor with low or no toxicity will be immensely useful in prevention as well as treatment of cancer. Numerous Plk1 inhibitors are in development to evaluate their potential as treatments in oncology, some of them in preclinical and clinical phase I/II development (Schöffski, 2009; **Figure 3**). It will be interesting to determine whether enhancing APC/C mediated degradation of Plk1 yield similar therapeutic benefits as Plk1 inhibitors currently in clinical trials.

TARGETING APC/C^{Cdh1} ACTIVITY

Several lines of evidence suggest that modulation of the APC/C complex is a good anti-cancer therapeutic strategy. Downregulation of the catalytic subunits Apc2 and Apc11 leads to growth arrest and cell death in HeLa cells (Pray et al., 2002). Also, a small molecule, tosyl-L-arginine methyl ester (TAME), which binds to APC/C and prevents its activation by Cdc20 and Cdh1, produces mitotic arrest (Zeng et al., 2010; **Figure 3**). Furthermore, expression of several APC/C subunits is higher in tumor relative to normal tissue (Wang et al., 2003). Collectively, these studies suggest that pharmacological interference with APC/C activity through disruption of protein–protein interaction is likely to have potent anti-tumor activity (Pray et al., 2002; Huang et al., 2009).

Targeting upstream regulators of the APC/C complex controlling mitosis is also a promising strategy. Overexpression of APC/C inhibitors such as Emi1 in mammalian cells impedes cell cycle progression and results in cell death (Reimann et al., 2001). HDACs

Modulator	Therapy
HDACs	Vorinostat
HDAC I, HDAC II	Depsipeptide

APC/C Complex	Therapy
APC/C	TAME

Substrate	Therapy
Skp2	EB1089, RA, Troglitazone, CKI inhibition
Aurora A	Curcumin, Cyclic peptide ligands
Plk1	ZK-thiazolidinone, NMS-1, CYC-800, DAP-81, LC-445, others.

FIGURE 3 | Cancer therapeutics related to APC/C^{Cdh1}. Targeting the modulators, the APC/C^{Cdh1} complex or its substrates could be a good anti-cancer strategy. Some pharmacological treatments that regulate APC/C activity or substrate levels are currently in clinical trials or under development.

might directly target APC/C to ensure proper chromosome segregation and anti-tumor effects of HDAC inhibitors could be attributed to this deregulation (Kimata et al., 2008). There are emerging HDAC inhibitors that have been clinically validated as therapeutic agents in cancer patients with hematologic malignancies. Two HDAC inhibitors, vorinostat (pan-HDAC inhibitor) and depsipeptide (HDAC 1 and II inhibitor) have been approved by the FDA and are under further clinical investigation (**Figure 3**). HDAC inhibitors are well tolerated and clinically effective against hematologic cancers (Duvic and Vu, 2007; Luu et al., 2008; Modesitt et al., 2008).

CONCLUDING REMARKS

The APC/C is a unique ubiquitin ligase since it possesses a distinct structure and interacts with specific E2 enzymes required for mediating substrate ubiquitination. Further, APC/C^{Cdc20} activity is essential *in vitro* and *in vivo*, suggesting that no other ubiquitin ligase can substitute for APC/C's role during mitosis (Li et al., 2007; Manchado et al., 2010). Similarly, APC/C^{Cdh1} activity is required

for cell cycle traverse, differentiation, placental formation, and for inhibiting tumorigenesis (Garcia-Higuera et al., 2008; Li et al., 2008). These exciting studies suggest that APC/C plays a large role in normal cell proliferation, which may be misregulated during cancer. Consistent with this notion are new studies linking APC/C substrates and regulators to tumor formation. Thus, it may be attractive to modulate APC/C substrate or regulator interaction pharmacologically to ablate tumor growth, which would have the advantage that specific interactions relevant to a cancer type can be uniquely targeted.

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