

The anaphase-promoting complex/cyclosome: APC/C

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The major ubiquitin ligase required for mitosis is the anaphase-promoting complex/cyclosome (APC/C). This unusually complex E3 ubiquitin ligase targets cell-cycle-related proteins such as cyclins and securin for degradation by

the proteasome in mitosis and meiosis. The APC/C is regulated by phosphorylation, as well as by various activators and inhibitors that alter its substrate specificity at different phases of the cell cycle. Such tight control ensures appropriately timed degradation of key cell-cycle regulators.

The APC/C in the ubiquitin-proteasome pathway

E3 ubiquitin ligases represent the last step of a three-enzyme cascade that tags substrates with ubiquitin chains. First, in an ATP-dependent reaction, a unique ubiquitin-activating enzyme (E1) binds to and activates ubiquitin. Ubiquitin is then transferred to one of several ubiquitin-conjugating enzymes (E2s) that, together with an E3, transfer the ubiquitin onto a lysine residue of the substrate. This reaction is repeated, such that other

ubiquitins are progressively added onto the Lys48 residue of the preceding ubiquitin. In vivo, this reaction needs to be highly processive and targets the substrate for proteasomal degradation. The E2s that act with the APC/C in vitro are UbcH10/E2-C and UbcH5/Ubc4, but it is the E3 that confers most substrate specificity (Farras et al., 2005; Pickart, 2004).

The APC/C is a RING-type E3. These contain a RING zinc-finger domain that binds the E2 and both recruits the E2 to the substrate and acts as a cofactor to enhance substrate modification.

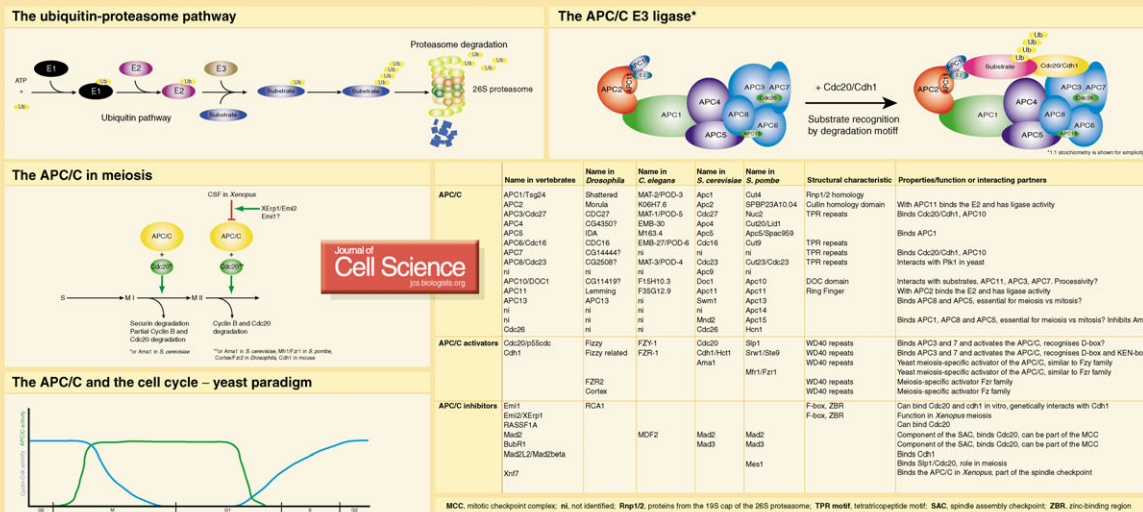
APC/C regulation

APC/C activators

The APC/C associates with activators from the Cdc20/Fizzy (Fzy) and Cdh1/Fizzy-related (Fzr) families in a

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cell-cycle-dependent manner. These activators are WD40 proteins and interact with the APC/C, potentially with APC3 and/or APC7. The binding to the APC/C involves a motif called the C-box, as well as a conserved isoleucine-arginine (IR) dipeptide in the C-terminus, which is important for Cdh1 but perhaps not for Cdc20 (Castro et al., 2005; Thornton et al., 2006).

In budding yeast mitosis, Cdc20 and Cdh1 bind sequentially to the APC/C, conferring different substrate specificities to the complex. Phosphorylation of Cdh1 by the cyclin-Cdk (cyclin-dependent kinase) complex Clb2-Cdc28 prevents its binding to the APC/C in G2 phase and during the first part of mitosis. When Cdk activity decreases, dephosphorylation of Cdh1 by Cdc14 allows it to bind the APC/C, and Cdc20 becomes itself a substrate of the APC/C. This is blocked by the mitotic exit network (MEN) (Peters, 1998). In mammalian systems, this sequential activation of the APC/C is less clear.

Two meiosis-specific activators of the APC/C have been identified in yeast: (1) *Schizosaccharomyces pombe* Mfr1, which functions at the end of meiosis II and degrades the remaining B-type cyclin (Cdc13) to reduce Cdk (Cdc2) activity (Blanco et al., 2001); and (2) Ama1, a *Saccharomyces cerevisiae* Cdc20 family member that is specifically expressed in meiosis and important for the first meiotic division. *Drosophila* has two meiosis-specific APC/C activators: Fzr2 and Cortex, which are exclusively expressed during spermatogenesis and oogenesis, respectively.

APC/C inhibitors

Before entry into mitosis, the APC/C must be inhibited to allow accumulation of mitotic cyclin-Cdk complexes. In animal cells, this is in part due to the F-box protein Rca1/Emi1. This protein probably blocks association of the APC/C with substrates. RCA1 in *Drosophila* interacts with Cdh1; Emi1, its mammalian homologue, can also bind Cdc20 in vitro. At the beginning of mitosis, Emi1 is phosphorylated and degraded by an Skp1-Cullin-F-box protein (SCF) E3 ligase complex. A relative of Emi1, Emi2/XErp1 appears

to inhibit APC/C^{Cdc20} in *Xenopus* meiosis II (Schmidt et al., 2005).

Mes1 is a meiosis-specific inhibitor of the APC/C in *S. pombe*. It directly binds and inhibits Slp1 (Cdc20) but has a function distinct from that of the checkpoint protein Mad2 (see below). Mes1 blocks the complete degradation of the B-type cyclin Cdc13 at anaphase I, allowing sufficient kinase activity to remain to initiate meiosis II. It is not clear what controls Mes1 activity (Izawa et al., 2005).

RASSF1A is a tumour suppressor that can interact with Cdc20 and inhibit the APC/C (Song et al., 2005). It might prevent premature cyclin degradation before the spindle checkpoint is set up; how its function is regulated is currently unclear.

The spindle assembly checkpoint

The spindle assembly checkpoint ensures that sister chromatids are equally divided between the two daughter cells at anaphase, blocking sister separation until each pair is correctly attached to microtubules emanating from opposite poles of the spindle. In mitosis, this checkpoint inhibits anaphase by preventing cyclin B and securin degradation, and responds to a signal generated by any improperly attached kinetochore. The ultimate mediators of this checkpoint are the checkpoint proteins Mad2 and BubR1 – as part of independent complexes or a single inhibitory complex called the mitotic checkpoint complex (MCC) that can bind Cdc20 (Bharadwaj and Yu, 2004; Musacchio and Hardwick, 2002; Yu, 2002; Zhou et al., 2002). The exact mechanism of APC/C inhibition is unclear, as is whether the APC/C could be modified by this signal. APC/C interacts with checkpoint proteins (Wassmann and Benezra, 1998) and co-localises with the checkpoint signal (Acquaviva et al., 2004).

In *Xenopus*, two other proteins are implicated in APC/C regulation. The ubiquitin ligase Xnf7, which binds and inhibits the APC/C (Casaletto et al., 2005), and Mad2L2, a relative of Mad2, which inhibits APC/C^{Cdh1} in vitro (Pfleger et al., 2001). However, it is not

clear whether these proteins have a conserved function.

Regulation of the APC/C by phosphorylation

A recent mass spectroscopy analysis of the complex in mammalian cells showed 42 phosphorylation sites, 34 of them mitosis specific (Kraft et al., 2003). In *Xenopus*, phosphatase treatment of extracts prevents APC/C activity, and mutation of potential Cdk1 phosphorylation sites in three budding yeast APC/C subunits delays progression through mitosis (Rudner and Murray, 2000). One function of phosphorylation is to regulate association with Cdc20. Other phosphorylations might finely tune APC/C activity. The main kinases involved are Cdk1 and polo-like kinase 1 (Plk1). In fission yeast, protein kinase A (PKA) negatively regulates APC/C but this might not be true elsewhere (Kraft et al., 2003). Clearly, other kinases could also be involved, such as those that are part of the mitotic checkpoint.

APC/C complex composition

The APC/C is conserved through evolution. The stoichiometry of its subunits is complex, and their spatial organisation is just beginning to be elucidated (Dube et al., 2005; Passmore et al., 2005; Thornton et al., 2006; Vodermaier et al., 2003). Our understanding of the individual subunits is mostly limited to the conserved structural motifs in their amino acid sequences.

The catalytic core

APC2 and APC11 form the enzymatic core of the complex. They harbour a cullin and a RING-finger domain, respectively. By analogy to the structure of the SCF, APC2 and APC11 could form a two-subunit catalytic core that binds the E2. In vitro, APC2 and APC11 can transfer ubiquitin to a substrate, but this reaction has little substrate specificity and poor processivity.

'TPR' subunits

Four subunits – APC3, APC6, APC7 and APC8 – have several tetratricopeptide repeat (TPR) protein-protein interaction motifs. In vitro, those of APC3 and APC7 interact with the IR motifs of

Cdc20 and Cdh1. Moreover, the four TPR subunits contain most of the phosphorylation sites present in the APC/C (Kraft et al., 2003).

Structural components

Some subunits could have a scaffolding role. APC4 and APC5 might connect the enzymatic core to the 'regulatory' TPR subunits. However, these proteins might not necessarily be limited to such a role. APC9 (in yeast), Cdc26 and APC13 also seem to be required for the structure and/or stability of the APC/C. APC13 is more unusual because it seems to provide an essential meiosis-specific function (Hall et al., 2003; Passmore et al., 2003).

APC10

APC10 is not essential for the assembly of the APC/C but is required for APC/C activity in yeast. APC10 contains a DOC domain; these are found in several proteins involved in ubiquitylation reactions. APC10 could bind the APC/C through its interaction with APC3 via an IR motif. It could also be involved in substrate recognition (Carroll et al., 2005; Passmore et al., 2003) and has been implicated in the processivity of ubiquitylation (Carroll and Morgan, 2002).

APC15

Mnd2/APC15 is associated with the APC/C in proliferating cells and in meiosis until metaphase II but its role seems to be specific to meiosis. It prevents premature degradation of securin by APC/C^{Amal} and thus premature loss of cohesion in meiosis I. Its inhibitory activity might be regulated by phosphorylation in metaphase I, and degradation in anaphase. How it discriminates between Amal and the other APC/C activators is unknown (Hall et al., 2003; Oelschlaegel et al., 2005; Penkner et al., 2005).

The role of APC/C in mitosis and meiosis

Mitosis

In mitosis, the APC/C is crucial for the transition from metaphase to anaphase. Inhibition of the APC/C or Cdc20 arrests cells in metaphase. Securin degradation

is essential for mitotic progression in budding yeast and can be rescued by the deletion of the securin gene (*Pds1*). Securin degradation enables separase to cleave the cohesin complex that links sister chromatids. In some systems, such as animal cells, this is not the only requirement for the metaphase-anaphase transition, in part because mitotic cyclin-Cdk can inhibit separase. Degradation of cyclin A and cyclin B is necessary to downregulate the kinase activity of the Cdk and permits sister chromatid separation, disassembly of the mitotic spindle, chromosome decondensation, cytokinesis and reformation of the nuclear envelope.

The APC/C also induces the degradation of several proteins from prophase to telophase in mitosis, including motor proteins and kinases, and possibly Shugoshin (*Sgo1*), which is involved in protecting sister chromatid cohesion at the centromeres, (Pines, 2006; Wang and Dai, 2005). However, the requirement for protein degradation has only been addressed in a few cases.

APC/C^{Cdh1}-dependent degradation of the cyclins in G1 phase prevents the premature accumulation of these proteins and premature entry into S phase. Moreover, APC/C^{Cdh1} controls the degradation of other regulators of S phase (e.g. *Orc1*, *Cdc6* and *geminin*) to regulate replication origin assembly. Finally, the APC/C also inhibits the activity of the SCF E3 that controls the G1-S transition. One of its components, the F-box protein *Skp2*, is a substrate for the APC/C in cycling cells (Vodermaier, 2004).

Meiosis

Between meiosis I and meiosis II, Cdk activity and Cdc20 protein levels must be maintained and/or restored. In yeast, *Mes1* protects part of the cyclin B population from degradation. In *Xenopus*, 50-70% of cyclin B1 is protected from degradation in meiosis I through an unknown mechanism.

To ensure chromosome pairs and sister chromatids separate at distinct stages, meiosis I and meiosis II employ different cohesin complexes (*Rec8* and *Sccl*), factors protecting specific cohesin regions (*Sgo1*) and specific activators of the APC/C (*Amal* in *S. cerevisiae*,

Mfr1/Fzr1 in *S. pombe*, *Fzr2* and *Cortex* in *Drosophila*, *Cdh1* in mouse).

In vertebrates, meiosis II is characterised by a prolonged metaphase arrest. This is imposed by cytotostatic factor (CSF), which is proposed to inhibit the APC/C and involves *Emi2/XErp1* and/or *Emi1* in *Xenopus* oocytes (Schmidt et al., 2005).

Substrate recognition

Some motifs are important for substrate recognition by the APC/C. The destruction box (D-box) initially described in cyclin B drives ubiquitylation by APC/C^{Cdc20}. A second motif, the 'KEN-box', first characterised in Cdc20, is recognised by APC/C^{Cdh1}. Recently, several more degradation motifs have been identified, such as the A-Box and O-Box (reviewed by Castro et al., 2005). Some can bind directly to Cdc20 or Cdh1 independently of the APC/C, but their relevance in vivo is unclear.

Substrate recognition by the APC/C is probably not dependent only on Cdc20 and Cdh1. During the embryonic *Drosophila* cell cycle, no Cdh1 is expressed but degradation of specific substrates is still temporally regulated. Moreover, substrates of Cdc20 or Cdh1 do not all disappear at the same time in mitosis – for example, APC/C^{Cdc20} ubiquitylates cyclin A in prometaphase before cyclin B in metaphase. Other subunits of the APC/C, such as APC10, might therefore be involved in substrate selection. Indeed, the cyclin B D-Box motif and the APC/C directly interact in *Xenopus* egg extracts (Yamano et al., 2004) and in *S. pombe* (Meyn et al., 2002). Substrates might thus cooperatively bind to Cdc20 or Cdh1 and the APC/C itself.

Strong evidence indicates that regulation of the localisation of substrates and the APC/C participates in substrate selection. In *Drosophila* and human cells, cyclin B degradation is spatially regulated and it appears to be localised to the spindle (Clute and Pines, 1999; Huang and Raff, 1999; Huang and Raff, 2002). Moreover, the subcellular localisation of the APC/C is regulated (Acquaviva et al., 2004; Huang and Raff, 2002; Melloy and Holloway, 2004; Topper et al., 2002; Yen, 2002) and the

inhibitory signal from the spindle assembly checkpoint could be restricted to specific cellular locations (Musacchio and Hardwick, 2002; Yen, 2002).

Perspectives

Although the central role of the APC/C in mitosis and meiosis is well established, it is still intensively investigated how it works and is regulated. One can presume that the complexity of its composition allows a sophisticated level of regulation necessary for it to fulfil its multiple tasks. Moreover, although we focus here on mitosis and meiosis, note that the APC/C is also active in differentiated, non-dividing cells such as neurons (Gieffers et al., 1999; Teng and Tang, 2005; van Roessel et al., 2004) and hepatocytes (Wirth et al., 2004), and plays important roles beyond cell division (for reviews, see Castro et al., 2005; Peters, 2002).

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