PERSPECTIVE

The role of Cdk7 in CAK function, a retro-retrospective

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Most transitions in the eukaryotic cell cycle are catalyzed by cyclin-dependent kinases (Cdks, CDKs), complexes formed between a member of the Cdk family of protein kinases and a regulatory cyclin subunit. CDKs are among the most highly regulated enzymes known: Their activities are controlled through multiple mechanisms that include cyclin association, positive and negative phosphorylation events, negative regulation through association with Cdk inhibitors (CKIs), and association with accessory proteins such as Cks/Suc1 (Fig. 1) (reviewed in Morgan 1997). In addition to controlling Cdk activation, the cyclin subunit may also contribute to substrate specificity. These elaborate regulatory pathways reflect the critical roles of cyclin-kinases in the life of a cell; alterations that generate unregulated cyclin-kinase activity can promote improper proliferation that can result in developmental defects or proliferative diseases such as cancer (Sherr 1996).

The Cdk subunit alone is inactive and requires both association with a cyclin and phosphorylation on a conserved threonine residue (T161 in human Cdc2 and T160 in human Cdk2) for full activation (Gould et al. 1991; Desai et al. 1992; Solomon et al. 1992; Connell-Crowley et al. 1993). In the case of Cdk2, these two events account for an increase in activity of greater than seven orders of magnitude (Connell-Crowley et al. 1993; Russo 1997). Cyclin A promotes Cdk2 activation by inducing two major structural changes in the kinase that are likely to be conserved in other cyclin/Cdk pairs (Jeffrey et al. 1996; Russo et al. 1996). First, cyclin binding leads to a conformational change in the amino-terminal PSTAIRE/helix that reorients the catalytic residue glutamate-51. This residue is conserved in all eukaryotic protein kinases and is involved in ATP binding. In addition, cyclin binding leads to a change in the orientation of the T-loop, the region of Cdk2 containing the activating threonine phosphorylation site T160. In the absence of cyclin, the T-loop blocks substrate access to the active site but the conformational changes induced by cyclin largely relieve this steric block. This conformational change in the T-loop may also be critical for the activating phosphorylation event because T160 is not particu-

larly solvent-exposed in monomeric Cdk2 but is well exposed in the cyclin/Cdk2 complex. Completion of the Cdk activation process involves phosphorylation of the T-loop threonine by Cdk activating kinase (CAK), a modification that promotes further structural changes in the T-loop (Russo et al. 1996).

Evidence for Cdk7/cyclin H as CAK

There has been an overwhelming interest in the elucidation of Cdk regulatory mechanisms since they ultimately control cell cycle transitions and, therefore, proliferations. This was particularly true for CAK since blocking this activation step would provide an effective means of inhibiting the activity of perhaps all Cdk complexes. The first indications of the existence of CAK came from the identification of an activity in *Xenopus* egg (Solomon et al. 1992) and mammalian cell extracts (Desai et al. 1992) that would activate Cdc2 through phosphorylation of T161, a process that requires prior association with cyclin B. Using Cdk activation as an assay, a CAK activity was purified from multiple systems and the activity was attributed to a complex between Cdk7 (originally referred to as MO15 in *Xenopus*) (Fesquet et al. 1993; Poon et al. 1993; Solomon et al. 1993) and cyclin H (Fisher and Morgan 1994; Mäkelä et al. 1994). This complex was subsequently shown to activate cyclin D/Cdk4 complexes (Matsuoka et al. 1994) and homologs in *S. pombe* were identified that displayed CAK activity in vitro (Buck et al. 1994; Damagnez et al. 1995). There was good reason to believe that this CAK activity constituted the major CAK in *Xenopus* and mammalian cells. First, there was no biochemical evidence for additional CAK activities distinct from those isolated, and their activity tracked as a single peak over several purification steps (Solomon et al. 1993; Fisher and Morgan 1994). Consistent with this, antibodies against XeCdk7 depleted CAK activity from egg extracts and XeCdk7 immune complexes contain CAK activity that phosphorylates Cdk2 specifically on T160 (Poon et al. 1993; Solomon et al. 1993; Fesquet et al. 1997). Second, recombinant Cdk7 and cyclin H alone can reconstitute CAK activity toward Cdc2 and Cdk2 (Fisher and Morgan 1994), providing strong evidence that the activity attributed to these proteins in purified fractions

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Figure 1. Multiple mechanisms regulate Cdk activity. Cdk activity is positively regulated (arrowheads) by association with cyclins, by phosphorylation on T161 by CAK, and by dephosphorylation by Cdc25 phosphatases. Cdk activity is negatively regulated by CKIs, Wee1-like kinases, and possibly by Kap1 phosphatase. The abundance of cyclins and some CKIs is regulated by transcriptional mechanisms and by ubiquitin-mediated proteolysis. The function of Cks1 is unknown but may involve substrate recognition.

resulted from the Cdk7/cyclin H complex. In contrast to expectations, Cdk7/cyclin H activity appears to be constitutive during the cell cycle (Poon et al. 1994; Tassan et al. 1994), suggesting that CAK is not used specifically to regulate specific cell cycle transitions, at least in a particular cell type under the conditions examined. Nevertheless, these findings were intriguing in that they demonstrated the involvement of a Cdk-based kinase cascade in cyclin-kinase activation.

Cdk7/cyclin H is unusual in that its activation can proceed through two distinct pathways. One pathway involves enhanced association of Cdk7 and cyclin H through an assembly factor referred to as p36^{MAT1} (Devault et al. 1995; Fisher et al. 1995; Tassan et al. 1995). In this case, MAT1 is a stable component of the CAK complex and activation proceeds without a requirement for phosphorylation of Cdk7 in its T-loop equivalent. MAT1 contains a RING finger domain, although assembly activity does not require this domain. An alternative pathway for activation requires phosphorylation of Cdk7 in its T-loop and this function can be provided by cyclin A/Cdk2 in vitro, suggesting a possible feedback loop in Cdk activation (Fisher et al. 1995).

Complications arise concerning the role of Cdk7/cyclin H as CAK

The early biochemical data supporting a role for Cdk7/cyclin H in Cdk activation was strong. However, this simple picture of Cdk7/cyclin H function was complicated by genetic and biochemical data demonstrating that the Cdk7 homolog in *Saccharomyces cerevisiae*, Kin28, has a role in transcription (reviewed in Fisher and Morgan 1996). Both the mammalian Cdk7/cyclin H/MAT1 complex and its most closely related budding yeast complex, Kin28/Ccl1 (Valay et al. 1993), were shown to be components of the basal transcription com-

plex TFIIF (Feaver et al. 1994; Roy et al. 1994; Serizawa et al. 1995; Shiekhataar et al. 1995; Valay et al. 1995; Svejstrup et al. 1996). TFIIF plays critical roles in both transcription initiation and in nucleotide excision repair and was known for some time to contain an activity capable of phosphorylating the RNA polymerase II carboxy-terminal domain (CTD). Thus the finding that a Cdk complex is a component of TFIIF immediately suggested that this kinase might contribute to CTD phosphorylation. Perhaps not surprisingly, Cdk7 activity in TFIIF complexes is required for transcription of some (but not all) promoters in vitro (Akoulitchiev et al. 1995; Mäkelä et al. 1995) and TFIIF-associated Cdk7 activity toward the CTD does not appear to be required for the initiation step in vitro (Akoulitchiev et al. 1995). Interestingly, cyclin/Cdk complexes are used in multiple contexts in transcription. For example, Cdk8/cyclin C is a component of the RNA polymerase holoenzyme and also acts as a CTD kinase in vitro (Liao et al. 1995; Leclerc et al. 1996; Rickert et al. 1996). Importantly, both free and TFIIF-associated Cdk7/cyclin H/MAT1 complexes exist in cell extracts, and the free Cdk7 complex has a higher specific CAK activity than the TFIIF complex (Drapkin et al. 1996; Rossignol et al. 1997; Yankulov and Bentley 1997). Nevertheless, the appearance of Cdk7/cyclin H as a component of TFIIF was sufficient to raise some doubt as to whether this kinase functioned as CAK in vivo.

Evidence against cyclin H/Cdk7 complexes acting as CAK in vivo

Although the suggestion that Cdk7/cyclin H might function in transcription did not rule out a role in direct Cdk regulation, it did raise the question of whether it really had two functions in vivo. Doubt concerning the role of the cyclin H/Cdk7 complex as a CAK in vivo was further compounded by genetic and biochemical data demonstrating that Kin28 has a role in transcription and is a CTD kinase, but is not required for Cdc28 phosphorylation in vivo and cannot act as CAK in vitro (Cismowski et al. 1995).

These findings led to a search for the actual in vivo CAK function in yeast. The answer came last year with the identification of a novel kinase Cak1 (also referred to as Civ1 for CAK in vivo) (Espinoza et al. 1996; Kaldis et al. 1996; Thuret et al. 1996). Although Cak1 was also identified based on its ability to phosphorylate Cdc28 and Cdk2 in an in vitro assay (Espinoza et al. 1996; Kaldis et al. 1996), mutational analysis of the CAK1 gene provided an in vivo verification that Cak1 is required for Cdc28 phosphorylation and activation. Temperature-sensitive mutations were identified that arrest at either the G1/S transition or the G2/M transition (Kaldis et al. 1996; Thuret et al. 1996), the two transitions that are most sensitive to defects in Cdc28 activation. Unlike Cdk7/cyclin H, Cak1 is active as a monomer and lacks CTD kinase activity. Although it is most closely related to the Cdk family of protein kinases, the kinase is un-

usual, in that it lacks 4 of the 12 signature motifs in protein kinases.

The return of Cdk7 as CAK

There are two simple explanations for the discrepancy concerning the identity of CAK. The first is that metazoans contain a *CAK1* homolog that is responsible for Cdk activation, and that Cdk7/cyclin H/MAT1 functions primarily in the context of TFIIF but has the ability to phosphorylate Cdks in vitro. The second explanation is that budding yeast utilize a distinct mechanism for Cdk activation and that Cdk7 is actually a bifunctional enzyme in larger eukaryotes, promoting both Cdk activation and transcription. At first glance, the possibility of a distinct mechanism in budding yeast seems unlikely. Most fundamental cell cycle control mechanisms are conserved throughout all eukaryotes. However, a recent genetic analysis of Cdk7 function suggests that the string of conserved cell cycle regulators may have just been broken with respect to CAK activity. An article in this issue of *Genes & Development* provides strong genetic evidence for a role of Cdk7 in Cdc2 activation in *Drosophila melanogaster* (Larochelle et al. 1997). Although the results in this paper do not rule out the existence of a *CAK1*-related gene in species other than budding yeast, they do promote the notion that one of the most fundamental aspects of Cdk activation occurs through distinct mechanisms in budding yeast and at least some metazoans.

Antibodies against DmCdk7 immunoprecipitate CAK activity toward Cdk2/cyclin A from embryo extracts. Most importantly, *cdk7^{null}* animals display defects in progression through the larval stage: Approximately half of the mutant animals die as larvae whereas the remainder die as pupae. Defects in cell proliferation are most pronounced in the imaginal discs where mitotic activity is high in the developing embryo. In contrast, there is no apparent defect in polyploid tissues where cells undergo multiple S phases without mitosis, a process that is thought to require cyclin E/Cdk2 (a.k.a. cdc2c). Consistent with a role in Cdc2 activation, these phenotypes closely parallel those seen in *Dmcdc2* mutants (Stern et al. 1993).

The effects on imaginal disc development in *cdk7^{null}* embryos, although consistent with a requirement for *cdk7* in cell proliferation, could be indirect. More definitive experiments came from the analysis of a conditional Cdk7 allele. *cdk7^{ts}* animals were shown to be viable at 18°C but inviable at 27°C (Larochelle et al. 1997). The mutant Cdk7 protein was not temperature-sensitive for CAK activity in vitro, but did show a progressive reduction in *cdk7* abundance over time in vivo. This complicates the analysis somewhat as the low levels of Cdk7 that persist may retain some activity. When shifted to restrictive temperatures, adult animals remain viable over an extended period of time but display defects in gamete production, the timing of which correlates with reduced *cdk7* protein. Similar gametogenesis defects were detected in *cdc2* mutants.

The analysis of *Dmcdk7* mutations is complicated by the possibility that this kinase is required not only for Cdk phosphorylation but may also be required for expression of proteins required for cell cycle progression, including cyclins, through its association with TFIIF. For example, in budding yeast, inactivation of Kin28 leads to reduced levels of Cdc28-dependent kinase activity not because of defects in Cdc28 phosphorylation but because of defects in cyclin gene transcription (Cismowsky et al. 1995). This issue was addressed in part by demonstrating that the total levels of A-, B-, and E-type cyclins remain high in *cdk7^{ts}* animals (Larochelle et al. 1997).

The availability of *cdk7^{ts}* alleles also provided an opportunity to examine the status of cyclin/Cdk complexes and activities in mutant animals. In contrast to mammals, *Drosophila* cyclins A and B form exclusive complexes with Cdc2 whereas cyclin E specifically interacts with Cdk2. Loss of *cdk7* function leads to decreased cyclin A-dependent kinase activity largely through dissociation of Cdc2 whereas decreased cyclin B-dependent activity correlates with decreased levels of T161-phosphorylated Cdc2. Reduced levels of Cdc2 phosphorylation in *cdk7^{ts}* mutants provides the strongest data to date linking Cdk7 function to Cdk activation. The results with cyclin A are in agreement with previous biochemical studies indicating a role for T161 phosphorylation in stabilization of cyclin A/Cdc2 complexes (Ducommun et al. 1991; Desai et al. 1995). Surprisingly, however, cyclin E-dependent kinase levels were not affected in the *cdk7^{ts}* mutant (Larochelle et al. 1997), consistent with the unimpaired endoreduplication of the null allele.

If Cdk7 controls Cdc2 activation in *Drosophila*, does it also have a role in transcription? One prediction would be that if Cdk7 plays a major role in transcription, its loss might have substantial effects on gene expression and affect many pathways, as Kin28 loss appears to do. In this regard, the ability to undergo multiple S-phases was used as an indirect argument for the absence of global effects on transcription with loss of *cdk7* function (Larochelle et al. 1997). However, given the fact that residual wild-type Cdk7 activity might remain in the mutants either from maternal stores or from incomplete inactivation of the *ts* allele, further studies are required to determine to what extent, if any, TFIIF function is altered in *cdk7* mutant animals. It should be noted that, in the absence of complete genome information, a Cdk7-related gene could carry out the transcriptional role.

CAK questions

The picture of CAK now emerging is that Cdk7 is likely to be a bifunctional protein in metazoans but that two proteins, Kin28 and Cak1, fulfill these functions in budding yeast. However this picture is only a rough sketch with many important details yet to be added. Is CAK really an integral component of the transcriptional apparatus? Is it regulated, and if so how? Will there be additional Cdk7- and Cak1-related molecules that differen-

tially regulate Cdks and transcription during development? And precisely what is the relationship between Cdk7 and the different Cdk/cyclin complexes in cells? If Cdk7/cyclin H is truly CAK, does it regulate cyclin E/Cdk2 activity in *Drosophila*? It is conceivable that Cdk2 regulation in *Drosophila* occurs through a distinct CAK, perhaps Cak1-related kinase (oh, the agony of an incomplete genome project). Alternatively, the answer may lie not in the CAK phosphorylation step itself but in its reversal, T160-dephosphorylation by the Kap1 phosphatase (Poon and Hunter 1995). This phosphatase binds and dephosphorylates Cdk2 and Cdc2, but only in the absence of cyclin, that is, after the cyclin subunit has been destroyed through ubiquitin-mediated proteolysis. Thus, the persistence of cyclin E-dependent kinase activity may reflect an inability to destroy the existing cyclin E, either because its destruction machinery is not active in G2, the likely arrest point, or possibly because its destruction requires cyclin A activity, which is absent in *cdk7* mutant cells. In the presence of cyclin E, Cdk2 would be inaccessible to Kap1 and maintain its activity despite the absence of Cdk7 activity. A trivial explanation for the results with cyclin E that also cannot be excluded is that Cdk7 has a higher specific activity for cyclin E/Cdk2 and that residual Cdk7 activity present at the nonpermissive temperature preferentially maintains Cdk2 in its activated state relative to Cdc2. Thus, it is conceivable that Cdk7 is the CAK for cyclin E/Cdk2 but the *in vivo* conditions were unable to reveal this. Only further studies will distinguish between these possibilities.

In arriving at a complete understanding of CAK biology, one must wrestle with the issue of why Cdk function evolved to require CAK activation in the first place. The most satisfying answer would be that CAK activity is regulated, but evidence supporting this explanation has been elusive. Although the CAK itself may not be regulated, its access to Cdks could be manipulated by Cdk binding proteins as has been suggested for the CK1 p27 (Kato et al. 1994). Because biochemical purification might obscure actual CAK regulation (the biochemical equivalent of the Heisenberg uncertainty principle), *in vivo* assays for CAK activity that do not depend on Cdks may need to be developed to explore *in vivo* CAK regulation. On the other hand, if CAK activity is simply constitutive and dictated by the presence of cyclin, then why did cyclins and Cdks not evolve the ability to allow cyclins to function fully in Cdk activation, leaving negative regulation to tyrosine phosphorylation and Cdk inhibitors? One possibility is that the effect of phosphothreonine on Cdk structure cannot be simply mimicked by any naturally occurring amino acid, which is also suggested by the finding that negatively charged amino acids will not substitute for phosphothreonine in Cdk activation (Gould et al. 1991; Connell-Crowley et al. 1993).

Although these breakthroughs have certainly clarified the role of Cdk7 considerably, this defined break in the conservation of basic cell cycle regulators among eukaryotes is enough to send ripples of concern through any argument based on evolutionary conservation. In this

light, it should be noted that, although we now have strong evidence that Cdk7 is behaving as CAK in *Drosophila*, this does not necessarily mean that the same will hold true for mammals. However, for the time being we have reason to believe that Cdk7 has a good chance to be involved in Cdk regulation in all metazoans. Of course, we will just have to see how long this revised notion of cell cycle conservation holds.

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