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Human Cdc14A becomes a cell cycle gene in controlling Cdk1 activity at the G_2/M transition

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Cdc14 belongs to a dual-specificity phosphatase family highly conserved through evolution that preferentially reverses CDK (Cyclin dependent kinases)-dependent phosphorylation events. In the yeast *Saccharomyces cerevisiae*, Cdc14 is an essential regulator of late mitotic stages and exit from mitosis by counteracting CDK activity at the end of mitosis. However, many studies have shown that Cdc14 is dispensable for exiting mitosis in all other model systems analyzed. In fission yeast, the Cdc14 homolog Flp1/Clp1 regulates the stability of the mitotic inducer Cdc25 at the end of mitosis to ensure Cdk1 inactivation before cytokinesis. We have recently reported that human Cdc14A, the Cdc14 isoform located at the centrosomes during interphase, downregulates Cdc25 activity at the G_2/M transition to prevent premature activation of Cdk1-Cyclin B1 complexes and untimely entry into mitosis. Here we speculate about new molecular mechanisms for Cdc14A and discuss the current evidence suggesting that Cdc14 phosphatase plays a role in cell cycle control in higher eukaryotes.

Key words: cell cycle, mitosis, phosphatases, CDK, Cdc25, Cdc14

Abbreviations: APC, anaphase promoting complex; CDK, cyclin dependent kinases; FEAR, cdc fourteen early anaphase release network; MEN, mitotic exit network; rDNA, ribosomal DNA

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Many cellular processes in eukaryotes are controlled by reversible protein phosphorylation. This post-translational modification is controlled by kinase and phosphatase activities. Cell cycle progression is one such process, in which multiple independent regulatory steps, controlled by the action of kinases and phosphatases on key substrates, are involved. Among the kinases, the cyclin-dependent protein kinase 1 (Cdk1) associated with B type cyclins plays a crucial role, since it drives mitotic entry and progression through the early events of mitosis until all chromosomes have aligned at the metaphase plate. Following this, entry into anaphase and progression through late mitotic stages requires the inactivation of Cdk1 and the dephosphorylation of most of its substrates.[1,2] Cdk1-Cyclin B1 complexes activity is, therefore, strictly controlled.

The activation of Cdk1-Cyclin B1 at the entry into mitosis depends on both phosphorylation and dephosphorylation processes. Thus, for full activity Cdk1 needs to be phosphorylated by Cdk-activating kinase on its T loop.[3] In addition, inhibitory phosphorylations at the ATP-binding site (T14 and Y15) carried out by Wee1 and Myt1 kinases at G_2[4] have to be eliminated. This occurs at the G_2/M transition, when the activity of Cdc25 phosphatases, Cdc25A, Cdc25B and Cdc25C, exceeds that of the opposing kinases Wee1 and Myt1.[4] Active Cdk1-Cyclin B1 complexes then stimulate their own activation by directly activating Cdc25 phosphatases and inhibiting Wee1 and Myt1 kinases. Moreover, a remarkably complex network of different kinases and phosphatases also controls these positive and negative Cdk1 regulators. The result is the timely and spatially accurate activation of the Cdk1-Cyclin B1 complexes, responsible for the entry into mitosis and progression through the early mitotic stages.[5-8] In contrast, Cdk1 has to be inactivated at the metaphase-anaphase transition to allow progression through late mitotic phases. Moreover, the ordered dephosphorylation of Cdk1-Cyclin B1 substrates and APC (Anaphase Promoting Complex)-mediated proteolysis of mitotic regulators

govern the final mitotic stages and allow exit from mitosis.[2] In the budding yeast *Saccharomyces cerevisiae*, many key mitotic substrates of Cdk1 are dephosphorylated by Cdc14, a dual-specificity phosphatase that constitutes an essential regulator of late mitosis in this organism. Extensive genetic and biochemical studies have contributed to characterizing its numerous roles at the end of mitosis as well as its strict regulation in both space and time.[9-11] Cdc14 remains sequestered in the nucleolus from G_1 until metaphase. In anaphase, Cdc14 is released by the consecutive action of two regulatory cascades—the Cdc Fourteen Early Anaphase Release (FEAR) network and the Mitotic Exit Network (MEN),[9]—to reach a number of nuclear and cytoplasmic substrates. In this organism, Cdc14 triggers Cdk1 inactivation at the end of mitosis through the dephosphorylation of both the Cdk1 inhibitor Sic1 and its transcription factor Swi5, resulting in Sic1 accumulation and activation, and also through dephosphorylation of the APC activator Cdh1, responsible for mitotic cyclin degradation.[12] Moreover, multiple events during anaphase such as the localization of chromosomal passenger proteins to the spindle midzone, the regulation of spindle dynamics, the inhibition of ribosomal DNA (rDNA) transcription and the contribution to the accurate segregation of rDNA and telomeric regions,[13-23] as well as cytokinesis,[24] are also regulated by Cdc14. All these functions make this phosphatase essential for regulation of late mitotic events and the exit from mitosis in budding yeast.

Cdc14 is highly conserved through evolution and Cdc14 homologs have been identified in a wide range of organisms ranging from yeast to mammals. However, the control of mitotic exit by Cdc14 seems to be exclusive to budding yeast. In the fission yeast *Schizosaccharomyces pombe*, the Cdc14 homolog Flp1/Clp1 is a non-essential protein. However, cells lacking *flp1/clp1* gene are advanced in mitosis and divide at reduced size as a consequence of a cell cycle defect.[25,26] As in *S. cerevisiae*, Flp1/Clp1 localizes predominantly to the nucleolus during interphase, but it also resides at the spindle pole body. As cells enter mitosis, Flp1/Clp1 is released from the nucleolus and localizes to the nucleus, the mitotic spindle, the spindle pole bodies and the medial ring.[25,26] During early mitosis, Flp1/Clp1 is inhibited by Cdk1 phosphorylation until the end of mitosis, when it becomes activated by self-catalyzed dephosphorylation.[27] Flp1/Clp1 is not required for mitotic exit, but it does contribute to Cdk1 inhibition in late mitosis by dephosphorylation, and hence degradation of the Cdk1 activating protein Cdc25. Consequently, Flp1/Clp1 coordinates cytokinesis with cell cycle progression.[28-30] Additional functions of Flp1/Clp1 are its contribution to chromosome segregation, the regulation of spindle midzone functions, and full activation of the checkpoint response to replicative stress.[31-33]

The mammal genomes encode two Cdc14 isoforms, Cdc14A and Cdc14B, and in hominids, a third isoform, Cdc14Bretro/Cdc14C, which is very similar to Cdc14B, is originated from a retrogene.[34] Given the important roles of Cdc14 phosphatase in yeast, human Cdc14 homologs have been addressed in many functional studies aimed at shedding light on their molecular functions. Human Cdc14A complements the lack of Cdc14 in *S. cerevisiae*.[35] Moreover, both human Cdc14A and Cdc14B isoforms are able, although through different molecular mechanisms, to rescue Flp1/Clp1-deficient fission yeast cells,[36] indicating that some functional homology exits among human and yeast Cdc14 proteins.

Human Cdc14A, which is preferentially centrosomal in interphase, has been implicated in the regulation of centrosome replication, and consequently in chromosome segregation and cytokinesis.[37,38] Human Cdc14B, whose localization is mainly nucleolar during interphase, has been implicated in several specific functions, including mitotic exit,[39] nuclear organization,[40] mitotic-spindle assembly,[41] centriole duplication,[42] regulation of the G_1 phase length,[43] and also in the G_2 DNA damage checkpoint efficiency.[44] Moreover, certain other functions have been suggested for both Cdc14A and Cdc14B isoforms. Thus, the two human Cdc14 phosphatases are able to regulate PR-Set7 histone methyltransferase degradation at the end of mitosis, which seems to be necessary for proper mitotic progression.[45] Moreover, the results of a recent study using cell lines in which Cdc14A or Cdc14B genes were deleted by gene targeting suggest that both phosphatases are required for efficient DNA repair.[46] Surprisingly, however, these knockout cells did not display any other phenotype corresponding to the above mentioned Cdc14 functions, which were elucidated by RNA interference (RNAi)-mediated silencing experiments.[46] Different reasons could explain these discrepancies, among others the total versus partial depletion of the protein, the functional redundancy between Cdc14 isoforms or with other phosphatases, the genetic background of the cell type used, as well as the phase of the cell cycle when the protein depletion comes into effect. New studies are needed to shed light on the probably numerous roles of Cdc14 in higher eukaryotes. Furthermore, several targets of Cdc14A and/or Cdc14B, some of them validated both in vivo and in vitro, have also been identified, suggesting their potential contribution to a number of different molecular functions.[47-53] In view of this extensive number of findings, sometimes even controversial (reviewed in ref. 54), human Cdc14 phosphatases could be involved in many cellular processes; some specific to Cdc14A or Cdc14B isoforms, and other ones to both of them. The different localization of each isoform, centrosomal versus nucleolar/nuclear, suggests that they likely have different functions in the cell. However, at the time of mitosis both of them leave their corresponding subcellular localization and diffuse throughout the cell, gaining the opportunity to reach the same substrates, and to share some common functions, unless this possibility is limited by specific regulatory mechanisms for each isoform.

We have recently demonstrated that human Cdc14A modulates the timing of mitosis by inhibiting Cdk1-Cyclin B1 activity at the G_2/M transition.[55] Consistent with this cell cycle regulatory role, we found that cells depleted for Cdc14A accelerate their entry into mitosis. Based on the hypothesis that human Cdc14 homologs might down-regulate Cdc25 phosphatases, as their fission yeast counterpart does,[28,29] we found that Cdc14A interacts with and

dephosphorylates Cdc25B, inhibiting its activity. Moreover, Cdc14A also exerts an inhibitory effect on the catalytic activity of Cdc25A, even though this appears to be an indirect effect exerted by a still unknown protein[55] (**Fig. 1**). All Cdc25 isoforms appear hyperphosphorylated at the onset of mitosis (reviewed in ref. 56). The phosphorylation of Cdc25B by several kinases, including Cdk1-Cyclin B1, results in hyperactivation of its phosphatase activity. Cdc14A reverses Cdk1-Cyclin B1-dependent Cdc25B modification, preventing its full activation. In the case of Cdc25A, its phosphorylation is associated with the stabilization of this mitotic inducer by preventing its recognition by the ubiquitination machinery.[57] However the deregulation of Cdc14A affects the activity of Cdc25A at the G_2/M transition, suggesting a new mechanism of Cdc25A regulation based on changes in its catalytic activity indirectly modulated by Cdc14A.

Our work adds one more piece to the complex network that regulates Cdk1-Cyclin B1 activity at the time of entry into mitosis.[8] It has been reported previously that human Cdc14A, but not Cdc14B, is able to regulate *S. pombe* Cdk1 activity through the dephosphorylation and downregulation of SpCdc25 protein in cells lacking the *flp1/clp1*$^+$ gene.[36] Moreover, Xenopus Cdc14A can also dephosphorylate Cdc25, which might be its target in preventing the G_2/M transition in this organism.[58] These data suggest that regulation of the Cdc25s cell cycle phosphatases by Cdc14 could be an evolutionary conserved mechanism, and that the role of Cdc14 in CDK inhibition also exists in higher eukaryotes, although to control different cell cycle transitions. Supporting the latter notion, the *C. elegans* Cdc14 ortholog has been shown to participate in the maintenance of the G_1 cell cycle arrest of specific precursor cells by promoting the stabilization of the Cdk inhibitor CKI1.[59] Moreover, human Cdc14A can efficiently dephoshorylate Cdh1 and activate APC in vitro[48] and in vivo to regulate the ordered degradation of mitotic regulators at the end of mitosis.[60] All this evidence supports a role for Cdc14 in cell cycle control in multicellular organisms.

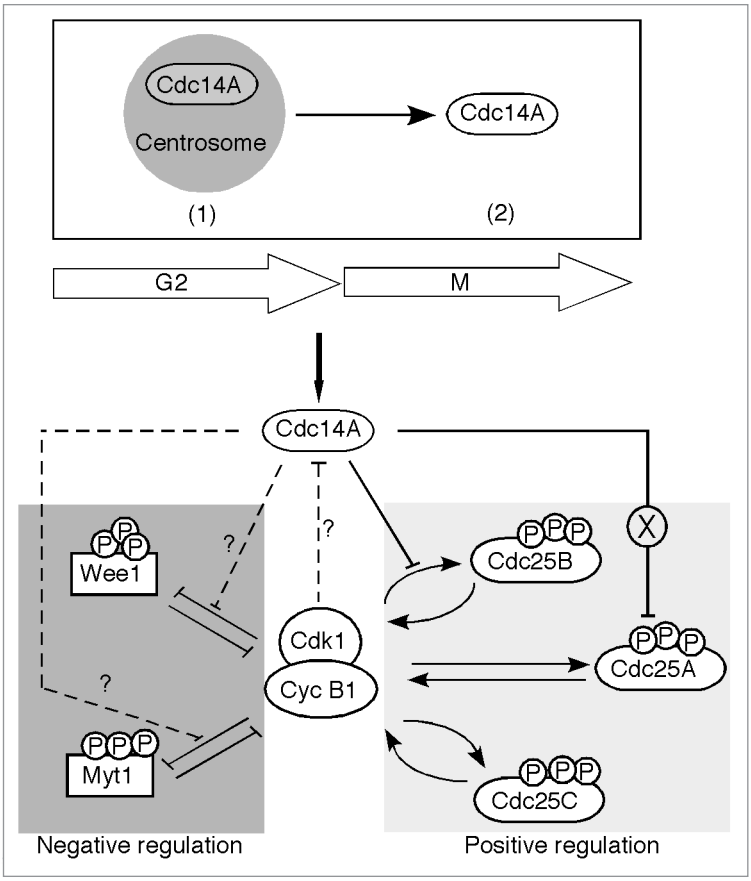

Figure 1. Working hypothesis of human Cdc14A phosphatase inhibiting Cdk1 activity at the G_2/M transition. Cdc14A is preferentially localized to the centrosome during interphase (1), and at the onset of mitosis it is released from the centrosome and diffuses throughtout the cell (2). Cdc14A reverses Cdk1-dependent Cdc25B phosphorylation and inhibits its catalytic activity. Moreover, Cdc14A also inhibits Cdc25A activity through an unknown mechanism. Consequently, Cdc14A interferes with the full activation of Cdk1-Cyclin B1 complexes at the G_2/M transition. We speculate that Cdc14A could also inhibit Cdk1-Cyclin B1 complexes activity through the Cdk1 inhibitory kinases Wee1 and/or Myt1. Moreover, a Cdk1-dependent inhibitory effect on Cdc14A could then allow full activation of Cdk1-Cyclin B1 complexes to enter into mitosis.

The finding of Cdc25 regulation by Cdc14A at the G_2/M transition raises important questions about the mechanisms regulating human Cdc14 phosphatases, which in turn may provide novel insights for understanding their physiological functions in mammals. An interesting issue is whether or not Cdc14A already controls Cdk1 activity on centrosomes, where Cdc14A and Cdc25B co-localize and where Cdc25B initiates the activation of Cdk1-Cyclin B1 complexes.[61-63] Upon analyzing Cdc25B in purified centrosomal extracts, we found that it is dephosphorylated in cells overexpressing Cdc14A (our own unpublished result), suggesting that Cdc14A is already acting at the centrosome to prevent the initial activation of Cdk1. However, another possibility is that the regulation of Cdc25A and Cdc25B could be performed by the pool of Cdc14A released from the centrosome at the G_2/M transition. The two possibilities are not mutually exclusive.

An even more interesting issue is whether Cdc14A could act on additional targets to regulate Cdk1 activity. The direct inhibitors of Cdk1, Wee1 and Myt1 kinases are potential candidates. At the entry into mitosis, Wee1 and Myt1 are directly regulated by Cdk1. Thus, the phosphorylation of Wee1 and Myt1 by Cdk1-Cyclin B1 complexes promotes the degradation of Wee1 and the inhibition of Myt1 kinase activity, thereby further amplifying Cdk1 activation.[64,65] Cdc14A could prevent the full activation of Cdk1 at the G_2/M transition by also reversing

these Wee1 and/or Myt1 inhibitory phosphorylations (**Fig. 1**).

It will be also interesting to find out whether or not Cdc14A is negatively regulated by Cdk1 phosphorylation just at the onset of mitosis, as has been found for the Flp1/Clp1 yeast homolog.[27] If this proves to be the case, in a normal cell cycle Cdc14A might inhibit Cdk1 activity at the G_2/M transition to avoid premature mitosis. Then, with a timely increase in Cdk1 activity, Cdc14A might be phosphorylated and inhibited by Cdk1 and/or other mitotic kinases while cells progress properly through the early stages of mitosis. At the end of mitosis, when Cdk1 activity starts to fall, Cdc14A might be activated again, probably by auto-dephosphorylation. Moreover, a Cdk1-independent regulation of human Cdc14A activity could promote additional functions specific to late mitosis. Whether these hypotheses apply to human Cdc14A mechanisms and regulation awaits elucidation.

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