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Cyclin-Dependent Kinase Inhibitors in Yeast, Animals, and Plants: A Functional Comparison

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ABSTRACT The cell cycle is remarkably conserved in yeast, animals, and plants and is controlled by cyclin-dependent kinases (CDKs). CDK activity can be inhibited by binding of CDK inhibitory proteins, designated CKIs. Numerous studies show that CKIs are essential in orchestrating eukaryotic cell proliferation and differentiation. In yeast, animals, and plants, CKIs act as regulators of the G1 checkpoint in response to environmental and developmental cues and assist during mitotic cell cycles by inhibiting CDK activity required to arrest mitosis. Furthermore, CKIs play an important role in regulating cell cycle exit that precedes differentiation and in promoting differentiation in cooperation with transcription factors. Moreover, CKIs are essential to control CDK activity in endocycling cells. So, in yeast, animals, and plants, CKIs share many functional similarities, but their functions are adapted toward the specific needs of the eukaryote.

KEYWORDS CKI, cell cycle, checkpoint, proliferation, differentiation

INTRODUCTION

The cell cycle consists of four phases: G1 phase, S phase (DNA replication), G2 phase, and M phase (mitosis and cytokinesis) and is remarkably conserved in all eukaryotes during evolution. In yeast, animals, and plants, the cell cycle is controlled by cyclin-dependent kinases (CDKs). The activation of CDKs requires binding with a cyclin (Pines, 1999), and activity of the CDK/cyclin complexes is regulated by phosphorylation and dephosphorylation of CDKs (Dunphy, 1994), by cell cycle-dependent proteolytic degradation of regulatory proteins (King *et al*., 1996; Peters, 1998), and by subcellular localization of the CDK/cyclin complexes (Ohi & Gould, 1999). Furthermore, CDK inhibitors (CKIs) can inhibit the activity of CDK/cyclin complexes (Sherr & Roberts, 1995, 1999).

During cell proliferation, specific checkpoints exist to control the proper order of the various cell cycle events. Three major checkpoints ensure the correct execution of the cell cycle progression (Figure 1). Cell cycle arrest can occur at the G1-S restriction point, at the G2-M transition, or at the metaphase-anaphase transition during mitosis. In addition, checkpoints also allow the cell

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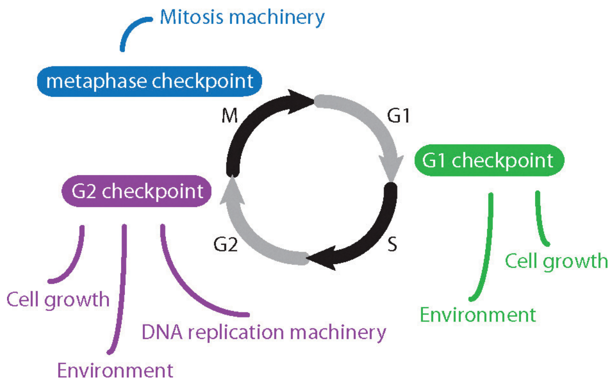

Figure 1 **Cell cycle checkpoints and signals ensuring correct cell cycle progression. Only when cell growth is sufficient and the environment is favorable, the G1 checkpoint allows transition from G1 to S. The G2 checkpoint permits transition from G2 to M only after completion of the DNA synthesis and when cell size is sufficient and the environment favorable. The metaphase checkpoint enables metaphase-anaphase transition only after the correct alignment of chromosomes on the spindle.**

cycle to be regulated by signals from the environment, such as nutrients, stress, or DNA damage. In unicellular organisms, nutrient availability is the most important factor determining cell growth, and hence, cell division occurs when cell size is sufficient. In multicellular organisms, different cell types perform divergent functions and regulation of cell division is more complex. Additional controls are needed to link entry into the cell cycle and cell cycle progression with internal and external signals. Furthermore, cell proliferation is only one aspect of development: cell growth, differentiation, and cell death influence the cell cycle process. Moreover, other types of growth control on the supracellular level (tissues and organs) evolved to regulate proliferation and development in complex organisms.

CKIs play key roles in the eukaryotic cell cycle by orchestrating cell proliferation and differentiation. To understand their roles, it is necessary to comprehend how they are regulated, both through the cell cycle and in response to extracellular signals.

Here, CKIs in yeast, animals, and plants are compared functionally. This comparison reveals similarities and differences in their functions and regulation and strengthens their importance in controlling cell cycle progression and in linking cell proliferation with differentiation. Furthermore, this review shows that CKIs in yeast, animals, and plants participate in conserved eukaryotic mechanisms, but with functional adaptations toward the specific needs of each type of organism.

FUNCTIONS OF CKIs DURING CELL PROLIFERATION

Yeast

The fission yeast, *Schizosaccharomyces pombe*, provides a very simple model of cell cycle regulation. *S. pombe* is capable of controlling its cell cycle with considerably fewer components than are used by other eukaryotes, including the budding yeast, *Saccharomyces cerevisiae*. *S. pombe* relies on a single CDK, Cdc2, to coordinate its mitotic cell cycle (Mendenhall, 1998). Cdc2/Cig2 and Cdc2/Cig1 complexes promote the G1-S transition (Mondesert *et al*., 1996), while the Cdc2/Cdc13 complex drives mitosis (Booher *et al*., 1989). The cyclins are regulated during cell cycle by transcription and ubiquitin-mediated proteolysis (Glotzer *et al*., 1991). The Cdc2 activity is further regulated by phosphorylation and dephosphorylation of specific amino acid residues (Lundgren *et al*., 1991) and by the CKI $p25^{Rum1}$ (Moreno and Nurse, 1994). $p25^{Rum1}$ plays a central role in maintenance of the G1 phase. By inhibiting the G1-S kinase activity, $p25^{Rum1}$ determines the timing of the G1-S transition by keeping cells in the pre-S(tart) state until they have acquired the minimal cell size necessary to initiate the cell cycle (Table 1). Additionally, $p25^{Rum1}$ is essential to prevent mitosis in cells that have not initiated DNA replication (Moreno and Nurse, 1994) (Table 1). Therefore, the protein levels of $p25^{Rum1}$ are tightly controlled by CDK phosphorylation and degradation through the SCF/ubiquitin-dependent proteolytic pathway (Benito *et al*., 1998). Moreover, $p25^{Rum1}$ is negatively regulated by mitogen-activated protein kinase (MAPK)-dependent phosphorylation. Degradation of $p25^{Rum1}$ does not depend on ubiquitination and is probably induced by conformational changes of the protein (Matsuoka *et al*., 2002). Gene expression of *p25*^{Rum1} is also regulated at the level of mRNA stability in response to nutrient deprivation (Daga *et al*., 2003).

In the budding yeast *S. cerevisiae*, a single CDK, Cdc28, regulates the cell cycle transitions by binding with different cyclin partners. Cln1, Cln2, and Cln3 are G1 cyclins, Clb5 and Clb6 are S phase cyclins and Clb1, Clb2, Clb3, and Clb4 are mitotic cyclins (Deshaies, 1997; Mendenhall and Hodge, 1998; Edgington and Futcher, 2001). Cyclin abundance during the cell cycle is controlled through transcription and ubiquitin-mediated protein degradation (Futcher, 1996; Breeden, 2000). In contrast to fission yeast, budding yeast

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TABLE 1 **Functions of CDK inhibitors (CKIs) in yeast, animals and plants during cell proliferation**

Kingdom	Species	CKI	Function(s)
Yeast	*Schizosaccharomyces pombe*	p25^{Rum1}	Inhibition of Cdc2/Cig1–2 complexes to prevent G1-S transition until cell growth is sufficient Inhibition of Cdc2/Cdc13 complexes to prevent mitosis in cells without DNA replication
	Saccharomyces cerevisiae	p40^{Sic1}	Inhibition of Cdc28/Clb5–6 complexes to prevent G1-S transition in response to cell size, stress, and nutrient starvation Inhibition of Cdc28/Clb1–4 complexes to assist in exit from mitosis and to establish a G1 phase
Animals	*Caenorhabditis elegans*	cki-1	Arrest of cells in G1 prior to later proliferation
	Drosophila melanogaster	Roughex	Inhibition of CDK1-cycA complexes to assist in exit from mitosis and to establish a G1 phase
	Xenopus leavis	p27^{Xic1} and p28^{Kix1}	Inhibition of CDK2-cycE and CDK2-cycA complexes to arrest the mitotic cell cycle
	Mammalia	p16^{Ink4a}, p15^{Ink4b}, p18^{Ink4c}, and p19^{Ink4d}	Binding of CDK4 and CDK6 to prevent G1-S transition
		p21^{Cip1}, p27^{Kip1}, and p57^{Kip2}	Inhibition of CDK4/6-cycD, CDK2-cycE, CDK2-cycA complexes to arrest G1-S transition
		p21^{Cip1} and p27^{Kip1}	Inhibition of CDK1-cycA complexes to assist in mitotic exit and to establish a G1 phase
Plants	*Arabidopsis thaliana*	KRP1—KRP7	Inhibition of CDKA;1-CYCD complexes to arrest the mitotic cell cycle
	Nicotiana tomentosiformis	NtKIS1a	Inhibition of CDK-CYCD complexes to arrest the mitotic cell cycle
	Zea mays	KRP1 and KRP2	Inhibition of CDK-CYCD and CDK-CYCA complexes to arrest the mitotic cell cycle

relies on three CKIs to ensure mitotic cell cycle and differentiation: p40^{Sic1}, Far1 and Pho81 (Mendenhall & Hodge, 1998). The budding yeast CKI p40^{Sic1} and the fission yeast CKI p25^{Rum1} show weak similarity in their inhibitory domains (Sánchez-Díaz *et al*., 1998). Although neither fission yeast nor budding yeast CKIs have sequence homology with the mammalian CKIs (Sherr & Roberts, 1995, 1999), p40^{Sic1} shares a structurally conserved inhibitory domain with p27^{Kip1} (Barberis *et al*., 2005), and Pho81 shows structural similarity to the Ink4 proteins (Ogawa *et al*., 1993).

The CKI p40^{Sic1} functions during cell proliferation by preventing premature S phase initiation until Cdc28 and Cln1-2 levels have risen sufficiently to complete bud initiation and spindle pole body duplication (Schwob *et al*., 1994) (Table 1). Therefore, p40^{Sic1} inhibits Cdc28/Clb5–6 complexes until it is destroyed by SCF^{Cdc4}/ubiquitin-dependent proteolytic degradation initiated by Cdc28/Cln1-2–dependent phosphorylation (Feldman *et al*., 1997; Nash *et al*., 2001) (Figure 2A). Furthermore, the budding yeast CKI p40^{Sic1} is involved in keeping the Cdc28/Clb5–6 complexes inactive in response to stress and nutrient starvation (Rowley *et al*., 1993; Gallego *et al*., 1997).

The second function of p40^{Sic1} is the regulation of exit from mitosis and the establishment of a G1 phase (Donovan *et al*., 1994). In budding yeast, CDK activity has to be inactivated in late anaphase to telophase to leave mitosis (Figure 2A). This inactivation of CDK activity is accomplished through inhibition of Cdc28/Clb1–4 activity by p40^{Sic1} and through proteolysis of mitotic cyclins by the anaphase-promoting complex (APC) (Donovan *et al*., 1994; Toyn *et al*., 1997) and is promoted by Cdc14 phosphatase. Cdc14 stimulates *p40^{Sic1}* transcription by dephosphorylation of its transcription factor Swi5 and promotes p40^{Sic1} accumulation by its dephosphorylation to prevent its degradation (Visintin *et al*., 1998). Degradation of Clb cyclins is activated by Cdc14 through dephosphorylation of the APC-specific factor Cdh1 (Zachariae *et al*., 1998).

The second CKI Far1 is not required for cell cycle progression, but is needed for cell cycle arrest and differentiation in response to mating pheromones

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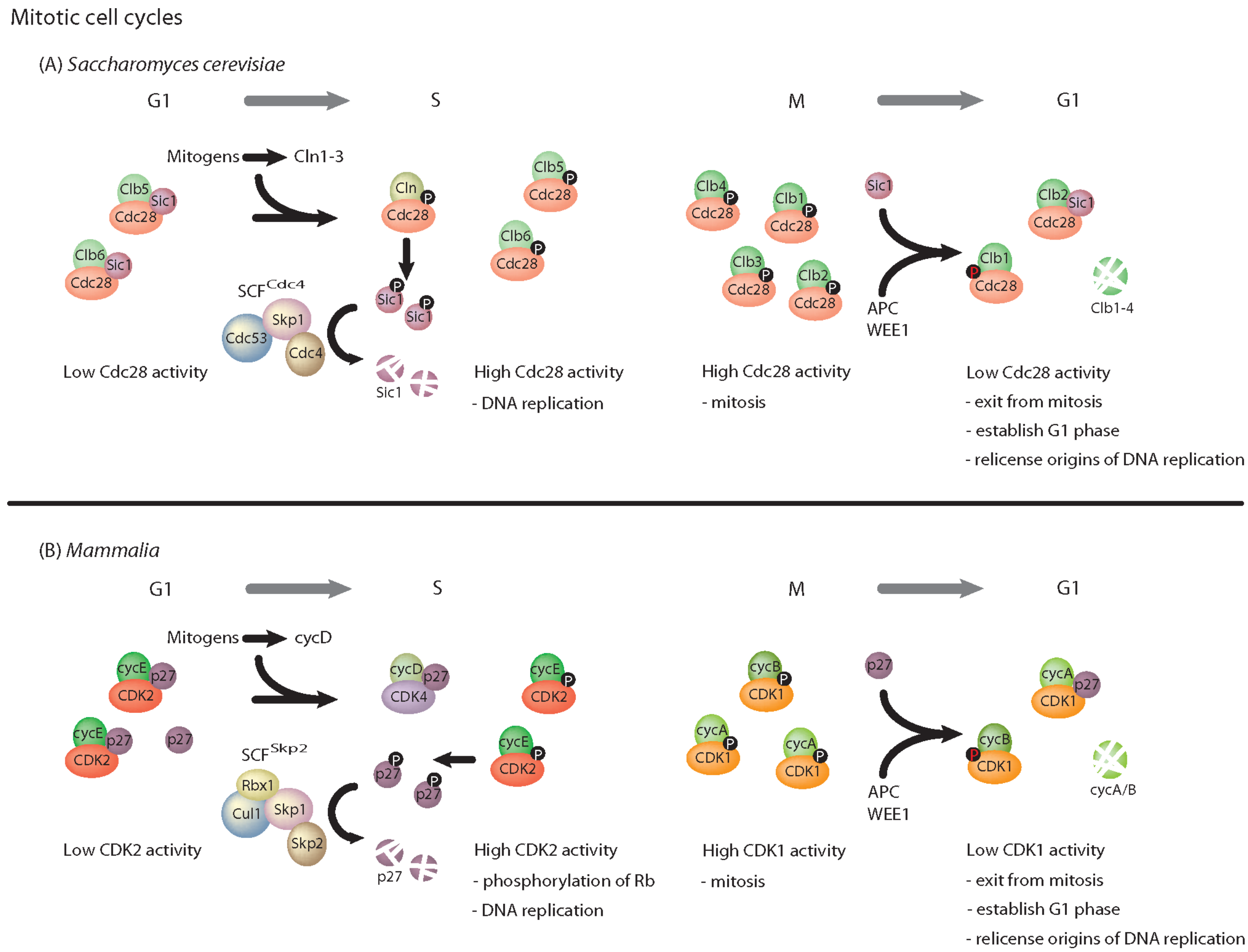

Figure 2 **Regulation of CDK activity by CKIs during mitotic cell cycles. (*A*) During the G1 phase, the *S. cerevisiae* CKI p40^{Sic1} inhibits the Cdc28/Clb5-6 complexes until mitogens activate the transcription of *Cln1-3* cyclins. Active Cdc28/Cln1–2 complexes phosphorylate p40^{Sic1} and phosphorylation triggers its degradation by the SCF^{Cdc4}/ubiquitin-dependent proteolytic pathway. Destruction of p40^{Sic1} releases the Cdc28/Clb5-6 complexes from the p40^{Sic1} inhibitory control and the active complexes can drive DNA replication. During late anaphase to telophase, mitotic Clb1-4 cyclins become degraded by the APC. Remaining Cdc28/Clb1-4 activity is down-regulated by p40^{Sic1} and by inhibitory phosphorylation by WEE1. Low Cdc28 activity is required to leave mitosis, to establish a G1 phase and to re-initiate replication origins. (*B*) During the G1 phase, the mammalian CKI p27^{Kip1} inhibits CDK2-cycE complexes until mitogens activate the transcription of genes encoding D-type cyclins. Titration of p27^{Kip1} into CDK4/6-cycD complexes relieves CDK2-cycE from the p27^{Kip1} inhibitory constraint. Active CDK2-cycE complexes phosphorylate p27^{Kip1} to trigger its degradation by the SCF^{Skp2}/ubiquitin-dependent proteolytic pathway and drive DNA replication. During metaphase-anaphase transition, both CDK1-cycA and CDK1-cycB activities are down-regulated through destruction of the mitotic cyclins by the APC. CDK1-cycA activity is further inhibited by p27^{Kip1} (and p21^{Cip1}) and CDK1-cycB activity through inhibitory phosphorylation by WEE1. Low CDK1 activity allows exit from mitosis, establishment of a G1 phase, and re-initiation of replication origins.**

(Chang & Herskowitz, 1990) (Table 2). Finally, the CKI Pho81 inhibits CDK/cyclin complexes that control gene expression under low-phosphate conditions (Schneider *et al*., 1994).

Animals

The increased complexity of cell cycle regulation in animals might explain the higher number of CDKs and other cell cycle regulators than in yeast (Nigg, 1995). Invertebrates displaying fast embryogenesis, such as *Caenorhabditis elegans* and *Drosophila melanogaster*, are very useful to study the interplay between cell proliferation and differentiation. As they go through development, their cells progress through various types of cell cycles, including the embryonic cell cycle, mitotic or somatic cell cycle, endoreduplication cycle, and meiotic cell cycle (Figure 3). The machinery used for each cell cycle is adapted toward these individual cycles and varies in their requirements for cell cycle genes. During embryonic cell cycles, S and M phases oscillate without gaps (Figure 3A). These

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TABLE 2 **Functions of CDK inhibitors (CKIs) in yeast, animals, and plants during differentiation**

Kingdom	Species	CKI	Function(s)
Yeast	*Schizosaccharomyces pombe*	$p25^{Rum1}$	Exit from the mitotic cell cycle in response to pheromones and nutrient starvation
	Saccharomyces cerevisiae	Far1	Cell cycle exit in response to mating pheromones
Animals	*Caenorhabditis elegans*	cki-1	Normal embryonic cell cycle exit
	Drosophila melanogaster	Dacapo	Normal embryonic cell cycle exit
			Inhibition of CDK2-cycE complexes during endocycle to allow correct relicensing of the origins of replication
	Xenopus leavis	$p27^{Xic1}$ and $p28^{Kix1}$	Exit from the mitotic cell cycle and promotion of differentiation in cooperation with transcription factors
	Mammalia	$p16^{Ink4a}$, $p15^{Ink4b}$, $p18^{Ink4c}$, and $p19^{Ink4d}$	Exit from the cell cycle and terminal differentiation by inhibiting CDK4 and CDK6
		$p21^{Cip1}$, $p27^{Kip1}$, and $p57^{Kip2}$	Exit from the mitotic cell cycle and promotion of differentiation in cooperation with transcription factors
		$p57^{Kip2}$	Inhibition of CDK2-cycE and CDK2-cycA complexes during endocycle to allow correct relicensing of the origins of replication
Plants	*Arabidopsis thaliana*	KRP1 and KRP2	Inhibition of CDK activity to control the switch between the mitotic cell cycle and the endocycle
	Lycopersicon esculentum	KRP1	Inhibition of CDK activity in endoreduplicating tissues

embryonic cycles use maternal stockpiles deposited during oogenesis, making growth and gene expression unnecessary. At distinct times during embryogenesis, cells in different tissues, and even in different lineages within a single tissue, become postmitotic, while other cells start somatic cell cycles. During somatic or mitotic cell cycles, divisions depend on oscillating G1-S and G2-M activities (Figure 3B). The regulation of cell cycle events, such as the introduction of G1 and G2 phases and the timing of mitotic exit, is intrinsic to each cell lineage and responds to cell fate specification signals. Some cell lineages undergo endoreduplication cycles during which S and G (gap) phases oscillate (Figure 3C), thus doubling the DNA ploidy with each additional cycle. The meiotic cell cycle is constricted to the germ line cells. During meiosis, two rounds of chromosome segregation follow a single replication of the genome to produce haploid gametes (Figure 3D).

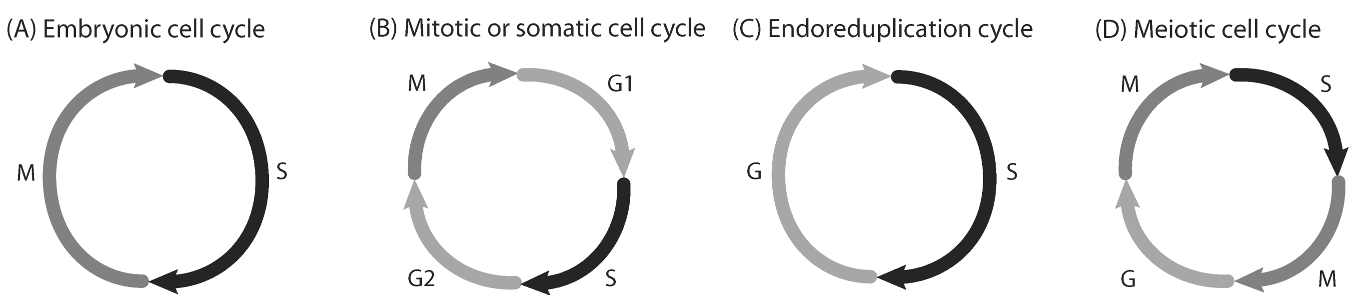

Figure 3 **Various cell cycle modes. (*A*) During embryonic cell cycles, DNA replication (S phase) and cell division (M phase) oscillate without intervening gap phases. (*B*) During mitotic or somatic cell cycles, DNA synthesis (S phase) and cell division (M phase) are separated by intervening gap phases (G1 and G2 phase). (*C*) During endoreduplication cycles, DNA replication (S phase) occurs without cell division resulting in increasing ploidy levels. Each round of DNA replication is followed by a gap phase (G phase). (*D*) During a meiotic cell cycle, one round of DNA synthesis (S phase) is followed by two rounds of cell division (M phase) separated by a gap phase (G phase).**

The nematode *C. elegans* has a single D-type cyclin, CYD-1, and a unique CDK-4 that are both required for postembryonic cell division to drive G1-S progression (Park & Krause, 1999). One E-type cyclin, CYE-1, has been identified in *C. elegans*, but a CDK2 ortholog has not been found yet (Seydoux *et al*., 1993). Only limited data are available to place CYE-1 in a G1 control pathway, but its genetic interactions are clearly different from those of CYD-1 (Boxem & van den Heuvel, 2001). A CDK1 ortholog, NCC-1, has been characterized that drives progression through mitosis (Boxem *et al*., 1999).

Two CKIs, cki-1 and cki-2, have been found in *C. elegans,* and both share homology to the mammalian Cip/Kip CKIs (Hong *et al*., 1998; Feng *et al*., 1999). A function has been assigned only to cki-1. Ectopic expression of *cki-1* causes cell cycle arrest in G1, while loss of function results in extra divisions in multiple cell lineages (Hong *et al*., 1998; Boxem & van den Heuvel, 2001; Fukuyama *et al*., 2003). Thus, cki-1 plays a role in the developmental regulation of G1-S progression throughout postembryonic development by keeping progenitor cells in G1 prior to later proliferation (Hong *et al*., 1998) (Table 1).

Cki-1 acts downstream of CDK-4/CYD-1 and mediates G1 arrest probably by inhibiting cyclin E kinase through direct association (Koreth & van den Heuvel, 2005). In response to extracellular signals, CDK-4/CYD-1 complexes may contribute to cki-1 inactivation by its sequestration in ternary complexes as suggested for the mammalian CDK4/6-cycD complexes (Polyak *et al*., 1994a; Toyoshima & Hunter, 1994). Different signals that depend on the cell type, the developmental stage, or the environment affect *cki-1* promoter activity (Hong *et al*., 1998). Additionally, posttranscriptional regulation of cki-1 involves Cdc14 phosphatase and cullin-2. Cdc14 acts upstream of cki-1, possibly dephosphorylating it, thereby promoting its stabilization to allow accumulation of cki-1, required for developmental arrest of cell division (Saito *et al*., 2004). Cullin-2 may function as an ubiquitin ligase to target cki-1 for degradation, because *Cul-2*-deficient germ cells show a posttranscriptional increase in the levels of cki-1, corresponding to a G1 arrest (Feng *et al*., 1999). Thus, proper temporal regulation of *cki-1* gene expression and protein accumulation controls lineage-specific and environmentally induced arrest of cell division (Hong *et al*., 1998).

In *Drosophila*, a D-type cyclin and a CDK4 homolog have been identified (Finley *et al*., 1996; Sauer *et al*., 1996). In contrast to *C. elegans*, the cyclin D regulates growth and is not necessary to drive G1-S transition (Datar *et al*., 2000; Meyer *et al*., 2000). The key regulator of G1-S transition in *Drosophila* is cyclin E. During early embryogenesis, cyclin E is constitutively present. Later, *cyclin E* transcription drops abruptly prior to G1 arrest preceding differentiation, but remains high in mitotically dividing cells. In endocycling cells, timing of the G1-S transition is regulated by cyclin E with *cyclin E* transcripts peaking prior to each S phase (Knoblich *et al*., 1994).

Two CKIs, Dacapo and Roughex have been characterized in *Drosophila*. While Dacapo shows sequence homology to the mammalian Cip/Kip inhibitors (de Nooij *et al*., 1996; Lane *et al*., 1996), Roughex shares only structurally conserved domains with the mammalian Cip/Kip inhibitors such as a nuclear localization signal and a cyclin-binding motif (Avedisov *et al*., 2001). Inhibition of CDK activity at the end of mitosis is achieved by the CKI Roughex (Foley *et al*., 1999) and by APC-mediated proteolysis of mitotic cyclins (Glotzer *et al*., 1991) (Table 1). Here, Roughex is required to allow exit from mitosis and to permit licensing of DNA replication origins. At the beginning of mitosis, Roughex is produced at levels that are insufficient to completely inactivate CDK1-cycA activity. However, cyclin A levels decrease rapidly during metaphase by cyclin proteolysis, and even low levels of Roughex become significant to promote the transition into anaphase (Foley & Sprenger, 2001). Furthermore, Roughex is needed for the establishment of a G1 phase by keeping CDK1-cycA activity low and is destroyed at the G1-S transition by the proteasome (Sprenger *et al*., 1997; Thomas *et al*., 1997). The budding yeast CKI $p40^{Sic1}$ also inhibits CDK/cyclin activity during exit from mitosis (Donovan *et al*., 1994). However, whereas $p40^{Sic1}$ acts during late anaphase to telophase, Roughex is involved in the metaphase-anaphase transition.

In vertebrates, several CDK/cyclin complexes play a role in cell cycle regulation. During cell cycle progression, D-type cyclins (D1, D2, and D3) are produced in a mitogen-regulated manner and these cyclins associate with and activate CDK4 or CDK6 (Matsushime *et al*., 1994). The expression of *cyclin E* is periodic during the cell cycle and CDK2-cycE kinase activity peaks at the G1-S transition (Koff *et al*., 1991; Lew *et al*., 1991) (Figure 2B). Active CDK4/6-cycD and CDK2-cycE

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complexes phosphorylate the retinoblastoma (Rb) family proteins, which repress the activity of the E2F family of transcription factors. Phosphorylation of Rb proteins releases E2F transcription factors that cause gene activation necessary for S phase entry. During S and G2 phases, CDK2-cycA activity increases progressively and regulates S phase transition. During G2 phase and mitosis, CDK1-cycA and CDK1-cycB activities increase and regulate G2-M transition and mitosis (Figure 2B).

In the African clawed frog (*Xenopus leavis*), two CKIs ($p27^{Xic1}$ and $p28^{Kix1}$) have been identified that show significant sequence similarity to the mammalian Cip/Kip inhibitors. $p27^{Xic1}$ and $p28^{Kix1}$ share 90% amino acid sequence identity with each other, preferentially inhibit CDK2-cycE and CDK2-cycA activities and bind with all CDK/cyclins and the proliferating cell nuclear antigen (PCNA) (Su *et al*., 1995; Shou & Dunphy, 1996) (Table 1). The mechanism that regulates $p27^{Xic1}$ levels in the *Xenopus* egg extract is unique among metazoan CKIs. Once $p27^{Xic1}$ is located in the nucleus, it does not have to bind to CDK2-cycE for ubiquitination. Additionally, $p27^{Xic1}$ phosphorylation is not essential for its ubiquitination in the egg extract (Chuang *et al*., 2005). The key to the regulation of $p27^{Xic1}$ ubiquitination lies within the C-terminal domain important for PCNA binding, indicating that PCNA plays an important role in the regulation of $p27^{Xic1}$ ubiquitination and its degradation (Chuang & Yew, 2005).

In mammals, two families of CKIs have been characterized according to their structures and CDK targets. The first, the Ink4 family, consists of four proteins: $p16^{Ink4a}$ (Serrano *et al*., 1993), $p15^{Ink4b}$ (Hannon & Beach, 1994), $p18^{Ink4c}$ (Guan *et al*., 1994; Hirai *et al*., 1995), and $p19^{Ink4d}$ (Chan *et al*., 1995; Hirai *et al*., 1995). The Ink4 proteins are composed of multiple ankyrin repeats and bind only CDK4 and CDK6. Generally, Ink4 proteins compete with D-type cyclins for binding to CDK4 or CDK6 (Parry *et al*., 1995, 1999; McConnell *et al*., 1999) (Table 1). However, these proteins are produced in a cell type-dependent manner. $p16^{Ink4a}$ accumulates progressively as cells age, possibly being induced by a senescence timer (Alcorta *et al*., 1996; Zindy *et al*., 1997). $p15^{Ink4b}$ is induced by TGF-β, which contributes to the ability of TGF-β to induce G1 phase arrest (Hannon & Beach, 1994; Reynisdóttir *et al*., 1995; Reynisdóttir & Massagué, 1997). $p18^{Ink4c}$ and $p19^{Ink4d}$ proteins are produced during embryogenic development with different tissue-specific patterns and remain at high levels in many adult tissues (Morse *et al*., 1997; Zindy *et al*., 1997; Phelps *et al*., 1998).

The second family of mammalian CKIs, the Cip/Kip family consists of three members: $p21^{Cip1}$ (Xiong *et al*., 1993; Dulić *et al*., 1994), $p27^{Kip1}$ (Polyak *et al*., 1994a, 1994b; Toyoshima & Hunter, 1994), and $p57^{Kip2}$ (Lee *et al*., 1995; Matsuoka *et al*., 1995). These proteins contain characteristic motifs within their N-terminal sequences that enable them to bind and inhibit CDK/cyclin complexes (Chen *et al*., 1995; Russo *et al*., 1996) (Figure 4).

$p21^{Cip1}$ has been identified independently with a number of different screening strategies (El-Deiry *et al*., 1993; Harper *et al*., 1993; Xiong *et al*., 1993; Jiang *et al*., 1994; Noda *et al*., 1994). $p21^{Cip1}$ has been shown to inhibit cell proliferation and ectopic expression of *p21^Cip1^* resulted in cell cycle arrest in G1 (Harper *et al*., 1995) (Table 1). The ability of $p21^{Cip1}$ to inhibit CDK/cyclin activity appears contradictory with its presence in most CDK/cyclin complexes in normal cycling cells. Furthermore, $p21^{Cip1}$ is induced when quiescent cells are stimulated to proliferate by mitogenic signals (Firpo *et al*., 1994). To explain this contradiction, a model has been proposed suggesting that kinase complexes associated with only one inhibitor molecule remain active and are inactivated in association with more than one inhibitor molecule (Zhang *et al*., 1994; Harper *et al*., 1995). This model was disposed of by the later finding that a single $p21^{Cip1}$ molecule is sufficient to completely inhibit CDK activity (Hengst *et al*., 1998). Binding of $p21^{Cip1}$ in complexes with cyclin D-dependent kinases is believed to relieve $p21^{Cip1}$ from CDK2-cycE, allowing CDK2-cycE activation later in G1 (Sherr & Roberts, 1999).

$p21^{Cip1}$ is mainly regulated transcriptionally (Gartel & Tyner, 1999), but also posttranscriptionally by mRNA stability (Macleod *et al*., 1995). Upon DNA damage, p53-dependent induction of *$p21^{Cip1}$* results in G1 arrest (El-Deiry *et al*., 1993; Dulić *et al*., 1994). $p21^{Cip1}$ contains two domains: an N-terminal CDK/cyclin-binding domain and a C-terminal PCNA-binding domain, thereby bridging the interaction between PCNA and CDK/cyclin (Chen *et al*., 1995). PCNA is a processivity factor for DNA polymerase Δ and interaction between PCNA and $p21^{Cip1}$ blocks DNA synthesis without affecting DNA repair (Zhang *et al*., 1993). Thus, the interaction of $p21^{Cip1}$ with PCNA might coordinate DNA replication and DNA

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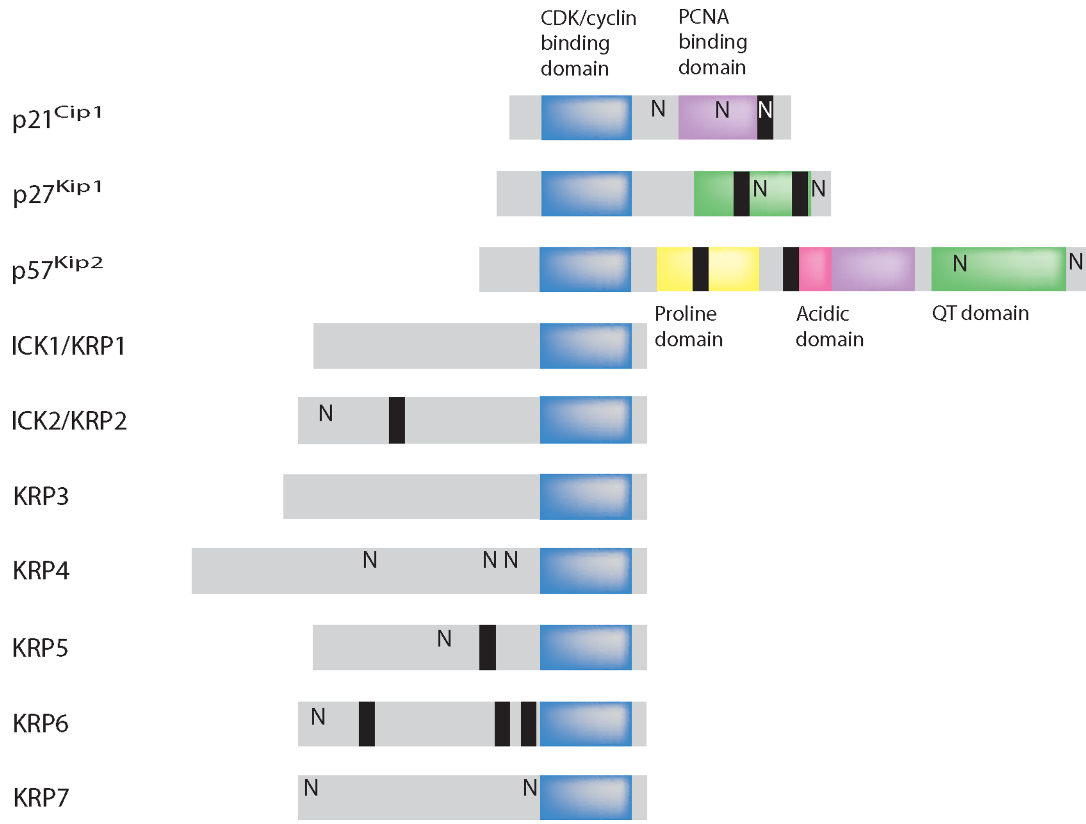

Figure 4 **Structural organization of the mammalian Cip/Kip inhibitors (p21^{Cip1}, p27^{Kip1}, and p57^{Kip2}) and of the *Arabidopsis* CKIs (ICK1/KRP1, ICK2/KRP2, KRP3, KRP4, KRP5, KRP6, and KRP7) showing only limited sequence identity in the CDK/cyclin-binding domain. *Black boxes* = PEST domains; *N* = nuclear localization signal.**

repair throughout the cell cycle. Extracellular signals, such as growth factors, cytokines, and a variety of agents that induce growth arrest and differentiation, activate *p21^{Cip1}* transcription by p53-independent mechanisms. These agents induce binding of different transcription factors to specific *cis*-acting elements located within the *p21^{Cip1}* promoter. One example is found in myoblasts shifted to medium containing a low concentration of serum. In these cells, the skeletal muscle-specific transcription factor MyoD activates both muscle-specific genes and *p21^{Cip1}* expression in a p53-independent manner (Halevy *et al*., 1995).

p27^{Kip1} has first been identified as a CDK2-inhibitory protein in contact-inhibited and TGF-β-treated cells (Koff *et al*., 1993; Polyak *et al*., 1994a, 1994b) and, subsequently, it has been cloned as a CDK4-cycD-interacting protein (Toyoshima & Hunter, 1994). p27^{Kip1} has been implicated as a mediator of various antimitogenic stimuli and plays a central role in the decision to either commit to the cell cycle or withdraw (Kato *et al*., 1994; Nourse *et al*., 1994; Polyak *et al*., 1994a) (Table 1).

Like p21^{Cip1}, p27^{Kip1} is also bound in cyclin D-dependent kinase complexes in proliferating cells (Toyoshima & Hunter, 1994). This observation suggests that CDK/cyclin complexes must overcome an inhibitory threshold of p27^{Kip1} to become active (Polyak *et al*., 1994a). When cells enter the cell cycle, cyclin D levels rise and CDK4/6-cycD complexes form. Subsequently, CDK4/6-cycD complexes sequester p27^{Kip1}, relieving CDK2-cycE complexes from its inhibitory constraint, thereby promoting CDK2-cycE activation later in G1 phase (Sherr & Roberts, 1999) (Figure 2B).

Both p21^{Cip1} and p27^{Kip1} bind and inhibit CDK1-cycA activity during mitotic exit. As a result, they assist in the extinction of the CDK activity required to allow exit from mitosis, establishment of a G1 phase, and relicensing of replication origins (Chibazakura *et al*., 2004) (Figure 2B). Similarly, the yeast CKI p40^{Sic1} and the *Drosophila* CKI Roughex are essential in regulating mitotic exit (Donovan *et al*., 1994; Foley *et al*., 1999; Foley & Sprenger, 2001).

Regulation of p27^{Kip1} is quite complex and happens on transcriptional, translational, and posttranslational

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levels. *p27^{Kip1}* is transcriptionally induced by the transcription factor AhR and inhibits cell proliferation (Kolluri *et al*., 1999). Regulation on the translational level is illustrated by the accumulation of p27^{Kip1} protein after the addition of antimitogenic stimuli, while the mRNA level remains constant (Hengst & Reed, 1996). On the posttranslational level, p27^{Kip1} protein accumulation depends on several mechanisms. At G1 phase, p27^{Kip1} is phosphorylated on Ser-10 by the human kinase interacting stathmin and exported from the nucleus by chromosome region maintenance 1 (CRM1)-mediated export in response to mitogenic signals. In the cytoplasm, p27^{Kip1} is ubiquitinated by the Kip1 ubiquitination-promoting complex ligase and degraded by the proteasome (Connor *et al*., 2003; Hengst, 2004; Kamura *et al*., 2004). During late G1 and S phases, p27^{Kip1} is phosphorylated on Thr-187 by CDK2-cycE, ubiquitinated in the nucleus by the ubiquitin ligase SCF^{Skp2}, and degraded by the proteasome (Pagano *et al*., 1995; Sheaff *et al*., 1997; Vlach *et al*., 1997; Nakayama *et al*., 2001) (Figure 2B). In conclusion, CRM1-dependent nuclear export and cytoplasmic degradation of p27^{Kip1} in early G1 allows activation of CDK2-cycE complexes, resulting in CDK2-cycE-mediated phosphorylation of p27^{Kip1} and its degradation in the nucleus, thereby promoting G1-S transition.

Because p21^{Cip1} and p27^{Kip1} have a high level of similarity in their primary structure, they are believed to inhibit their targets through similar mechanisms. p21^{Cip1} and p27^{Kip1} lack stable secondary or tertiary structures in free solution, enabling them to interact with several protein partners and to carry out diverse biological functions (Kriwacki *et al*., 1996; Lacy *et al*., 2004). Upon binding of the Cip/Kip protein, the cyclin subunit is first contacted by an α-helix, followed by a second α-helix that binds the CDK subunit, thereby mimicking the substrate, both in its position and in the contacts it makes to the active site groups. Thus, the insertion of the α-helix of the CKI into the catalytic cleft of the CDK directly blocks ATP binding (Russo *et al*., 1996; Pavletich, 1999).

p57^{Kip2} has been cloned simultaneously by two groups (Lee *et al*., 1995; Matsuoka *et al*., 1995) and is distinct from p21^{Cip1} and p27^{Kip1} by its unique domain structure and its gene expression in a tissue-specific manner (Lee *et al*., 1995). Ectopic expression of *p57^{Kip2}* in cell cultures caused cell cycle arrest in G1 phase (Lee *et al*., 1995) (Table 1). Targeted disruption of *p57^{Kip2}* in mice showed a role for this CKI in the control of the commitment/withdrawal decision as well as differentiation in particular tissues (Zhang *et al*., 1997). Like p21^{Cip1}, p57^{Kip2} contains a C-terminal PCNA-binding domain and the interaction between p57^{Kip2} and PCNA prevents PCNA-dependent DNA synthesis (Watanabe *et al*., 1998). p57^{Kip2} protein levels are regulated by SCF^{Skp2}/ubiquitin-mediated proteolytic degradation (Kamura *et al*., 2003).

Both the Ink4 and the Cip/Kip proteins play important roles in the development of cancer (Hirama & Koeffler, 1995; Kamb, 1998; Roussel, 1999; Ortega *et al*., 2002; Coqueret, 2003). However, we focus on a comparison between functions of CKIs in yeast, animals, and plants and therefore, the relationship between CKIs and cancer is beyond the scope of this review.

In vertebrates, two families of CKIs, the Ink4 and the Cip/Kip proteins, have evolved that share no sequence homology, although they bind to the same targets, CDK4 and CDK6. Additionally, whereas the Ink4 proteins form binary complexes with only CDK4 or CDK6, the Cip/Kip proteins form ternary complexes with CDK4-cycD, CDK6-cycD, CDK2-cycE, and CDK2-cycA. Individual *Ink4* and *Cip/Kip* genes show differential expression in response to different antiproliferative signals, in tissues, and during development. Taken together, these characteristics suggest that the two CKI families regulate distinct growth inhibitory pathways.

Plants

Plants have unique developmental features and although many mechanisms controlling the cell cycle are shared with other eukaryotes, numerous aspects of the plant cell cycle are specific. In plants, several classes of CDKs have been identified: CDKA, CDKB, CDKC, CDKD, CDKE, and CDKF (Joubès *et al*., 2000; Vandepoele *et al*., 2002). The first class, CDKA, is related to the yeast (Cdc2 and Cdc28) and mammalian (CDK1 and CDK2) CDKs and contains the PSTAIRE motif in the cyclin-binding domain. At the transcript and protein levels, plant CDKA is present throughout the cell cycle (Hemerly *et al*., 1993; Porceddu *et al*., 2001) and is involved in managing both G1-S and G2-M transitions (Hemerly *et al*., 1995; Porceddu *et al*., 2001). The second class, CDKB, is unique in plants and, unlike CDKA, its expression is strictly

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controlled by the cell cycle. CDKB is further classified into two groups: CDKB1 with the PPTALRE motif is present from S phase to mitosis, and CDKB2 with the PPTTLRE motif is produced in a more restricted period from G2 to M phase (Fobert *et al*., 1996; Magyar *et al.*, 1997; Umeda *et al*., 1999; Porceddu *et al*., 2001). In *Arabidopsis thaliana*, one CDKA and four CDKBs have been identified: Arath;CDKA;1, Arath;CDKB1;1, Arath;CDKB1;2, Arath;CDKB2;1, and Arath;CDKB2;2 (Vandepoele *et al*., 2002). Arath;CDKB1;1 activity has been shown to be essential for correct stomatal development (Boudolf *et al*., 2004a) and to be involved in inhibiting endoreduplication (Boudolf *et al*., 2004b). C-type and E-type CDKs are characterized by respectively PITAIRE and SPTAIRE motifs in their cyclin-binding domains (Joubès *et al*., 2000), but little is known about their functions. Arath;CDKC;1 and Arath;CDKC;2 are implicated in regulation of transcription (Barrôco *et al*., 2003), and Arath;CDKE acts in cell expansion of leaves and cell fate specification of floral meristems (Wang & Chen, 2004). Plant CDKD and CDKF comprise the CDK-activating kinases (CAKs) and the CAK-activating kinases (CAKAKs) (Umeda *et al*., 1998; Shimotohno *et al*., 2004). Arath;CDKD;3 and Arath;CDKD;4 interact with cyclin H and are closely related to the vertebrate CAK, CDK7. Arath;CDKF;1 works independently of cyclin H and, like a CAKAK, phosphorylates and activates Arath;CDKD;3 and Arath;CDKD;4 (Umeda *et al*., 2005).

For their activation, CDKs have to be associated with cyclins. A large number of cyclins have been identified in various plant species; for example, *Arabidopsis* has approximately 50 genes encoding cyclins (Vandepoele *et al*., 2002; Wang *et al*., 2004). Based on their sequence similarities, plant cyclins have originally been classified into three major groups: CYCA, CYCB, and CYCD (Renaudin *et al*., 1996). Later, other groups, such as CYCC, CYCH, CYCL, CYCP, and CYCT have been isolated in *Arabidopsis* and other species (Yamaguchi *et al*., 2000; Vandepoele *et al*., 2002; Barrôco *et al*., 2003; Wang *et al*., 2004). D-type cyclins regulate the G1-S checkpoint, work in a mitogen-dependent manner in association with CDKA (Riou-Khamlichi *et al*., 1999, 2000; Healy *et al*., 2001), and are possibly also involved in controlling the G2-M transition (Schnittger *et al*., 2002; Kono *et al*., 2003; Koroleva *et al*., 2004). A-type cyclins play a role in S phase and M phase control and are associated with CDKA and CDKB (Roudier *et al*., 2000). B-type cyclins affect G2-M transition and intramitotic cell cycle progression in conjunction with both CDKA and CDKB members (Weingartner *et al*., 2003, 2004). Plant cyclins form groups phylogenetically distinct from mammalian cyclins, suggesting that the cyclin function was not specified before the evolutionary divergence of the plant and animal lineages. Moreover, each group of plant cyclins contains more members than the equivalent group in animals. This observation probably reflects the ability of plants to respond to environmental and developmental signals in a plant-specific manner.

Additional cell cycle regulators have been detected in plants. In *Arabidopsis* they include: one Rb-related (RBR) protein, three E2Fs, two DPs, three DP-E2F-like (DEL) proteins (Vandepoele *et al*., 2002), a WEE1 kinase homolog (Sorrell *et al*., 2002), and a putative CDC25 phosphatase (Landrieu *et al*., 2004).

In *Arabidopsis*, seven CKIs have been characterized, the Inhibitor/Interactor of Cyclin-dependent Kinases (ICKs) or Kip-Related Proteins (KRPs) (ICK1/KRP1, ICK2/KRP2, KRP3, KRP4, KRP5, KRP6, and KRP7) that show only limited sequence similarity with the mammalian Cip/Kip inhibitors (Wang *et al*., 1997; Lui *et al*., 2000; De Veylder *et al*., 2001). Sequence homology is restricted to a region located at the extreme C-terminal end of each KRP (Figure 4). KRPs interact with CDKA;1 and with D-type cyclins (Schnittger *et al*., 2003; Zhou *et al*., 2003b), but not with B-type CDKs (Lui *et al*., 2000; De Veylder *et al*., 2001). Recently, KRPs have been shown to bind and inhibit CDKB2;1/CYCD2;1 complexes produced in insect cells, but these interactions need to be confirmed in plants (Nakai *et al*., 2006). Furthermore, they inhibit CDK activity *in vitro* (Wang *et al*., 1998; Lui *et al*., 2000; De Veylder *et al*., 2001) and in plants *in vivo* (Wang *et al*., 2000; De Veylder *et al*., 2001; Zhou *et al.*, 2002a) (Table 1). Transgenic *Arabidopsis* plants overexpressing *KRP* genes have a reduced CDK activity and show changes in plant morphology and development such as small and serrated leaves and modified flowers (Wang *et al*., 2000; De Veylder *et al*., 2001; Zhou *et al.*, 2002a). Microinjected KRP1 attenuates mitosis in living plant cells (Cleary *et al*., 2002). Additionally, targeting *KRP1* expression to developing petals results in the appearance of novel shapes in transgenic rapeseed (*Brassica napus*) plants (Zhou *et al*., 2002b). When *KRP1* was expressed during pollen development, pollen viability was affected, with male

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sterility as a consequence (Zhou *et al*., 2002b). The functions of the C-terminal and N-terminal domains have been determined for KRP1. Deletion analysis indicated that the conserved C-terminal domain is required for the interaction with CDKA;1 and CYCD3;1 (Wang *et al*., 1998) and further analysis confirmed that it binds CDK/cyclin complexes and regulates CDK activity. Furthermore, the N-terminal region was shown to increase KRP1 instability (Schnittger *et al*., 2003; Zhou *et al*., 2003a) and the central domain to be responsible for nuclear localization (Zhou *et al*., 2003a).

Arabidopsis KRP genes are regulated by plant hormones and show development- and tissue-specific expression patterns. *KRP1* expression is relatively low in all plant tissues, but is up-regulated by the plant hormone abscisic acid and by low-temperature treatments (Wang *et al*., 1998). Different expression profiles of the *Arabidopsis KRP* genes have been observed in different organs and in cell suspension cultures (Lui *et al*., 2000; De Veylder *et al*., 2001; Richard *et al*., 2001; Menges *et al*., 2005). *KRP2* is regulated transcriptionally by the plant hormone auxin and might play a role in preventing lateral root initiation (Himanen *et al*., 2002). The spatial expression of all seven *KRP* genes was analyzed by *in situ* hybridization on longitudinal sections of shoot apices of *Arabidopsis* plants (Ormenese *et al*., 2004). *KRP* genes could be divided into three groups according to their different expression patterns: expression of *KRP1* and *KRP2* was restricted to endoreduplicating tissues; that of *KRP4* and *KRP5* to mitotically dividing cells and that of *KRP3*, *KRP6,* and *KRP7* to both endoreduplicating and mitotically dividing cells. These results suggest different functions for the distinct KRPs. KRP1 and KRP2 might be involved in the establishment of polyploidy, KRP4 and KRP5 in regulation of the mitotic cell cycle, and KRP3, KRP6, and KRP7 in control of both the endoreduplication cycle and the mitotic cell cycle.

Little is known on how these proteins are regulated on the translational and posttranslational level. Only KRP2 has been shown to be controlled on the posttranslational level by proteasome-dependent degradation *in vitro* and *in vivo* (Verkest *et al*., 2005). Furthermore, *in vitro* analysis showed that proteolysis of KRP2 depends on phosphorylation by CDKs. Because the KRP2 protein level is higher in plants with reduced CDKB1;1 activity, KRP2 accumulation is probably regulated by CDKB1;1 phosphorylation (Verkest *et al*., 2005).

In tobacco (*Nicotiana tomentosiformis*) and maize (*Zea mays*), one (NtKIS1a) and two CKIs (KRP1 and KRP2) have been identified, respectively (Jasinski *et al*., 2002a, 2002b; Coelho *et al*., 2005). They all share sequence homology with the *Arabidopsis* KRPs and with the mammalian Cip/Kip inhibitors. Overexpression of *NtKIS1a* in *Arabidopsis* plants inhibits CDK activity and divisions, resulting in a significant reduction of growth (Jasinski *et al*., 2002b) (Table 1). The transgenic plants have a modified plant morphology with smaller organs that contain larger cells. The observed effects are similar to those in *Arabidopsis* plants overexpressing *KRP* genes (Wang *et al*., 1998; De Veylder *et al*., 2001; Zhou *et al.*, 2002a), thereby reflecting a common role in inhibiting CDK activity and cell division. Furthermore, overexpression of *NtKIS1a* restores normal development in *Arabidopsis* plants overexpressing *CYCD3;1*, indicating that NtKIS1a and CYCD3;1 can work together and antagonize each other (Jasinski *et al*., 2002b).

Maize KRPs are able to inhibit maize CDK/CYCD and CDK/CYCA complexes. Expression of Zeama; *KRP* genes results in reduced growth of embryonic maize calli (Coelho *et al*., 2005) (Table 1).

FUNCTIONS OF CKIs DURING DIFFERENTIATION

Yeast

In yeast, exit from the cell cycle and differentiation are driven by pheromone signaling or nutrient deprivation. In *S. pombe*, the CKI $p25^{Rum1}$ allows G1 arrest and initiation of sexual differentiation in the absence of nutrients or in response to pheromones (Daga *et al*., 2003) (Table 2). In *S. cerevisiae*, the CKI Far1 is required to arrest the cell cycle in the presence of mating pheromones (Chang & Herskowitz, 1990) by inhibiting Cdc28/Cln kinases (Peter & Herskowitz, 1994) (Table 2). Mating pheromones activate a MAPK signal-transduction pathway (Herskowitz, 1995) that stimulates transcription of *Far1* (McKinney *et al*., 1993) and prevents its degradation by phosphorylation (Henchoz *et al*., 1997). This makes Far1 unique among the known CKIs because its inhibitory activity is apparently enhanced by an inducible posttranslational modification (Tyers & Futcher, 1993). Thus, during cell proliferation and differentiation the budding yeast

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CKIs p40[Sic1] and Far1 have complementary functions that are completed by one single CKI, p25[Rum1], in fission yeast.

Animals

In animals, exit from cell proliferation and initiation of differentiation are determined by several opposing developmental signals and CKIs are key players in orchestrating these processes. The CKI cki-1 of the nematode *C. elegans* is essential for normal embryonic cell cycle exit in many cell lineages, demonstrating that it can control the time at which cells stop proliferating and differentiate (Table 2). Mammalian Cip/Kip inhibitors also regulate cell cycle exit preceding differentiation in response to antimitogenic stimuli and stress signals (Zhang *et al*., 1999). But, in contrast to mammalian development that is highly dependent on intercellular signals mediated by growth factors and cytokines, in embryos of *C. elegans* most cell types differentiate by cell-autonomous mechanisms (Sulston *et al*., 1983).

During embryonic development, the *Drosophila* CKI Dacapo controls the timing of withdrawal from the cell cycle in response to developmental signals (de Nooij *et al*., 1996; Lane *et al*., 1996) (Table 2). The accumulation of Dacapo and the down-regulation of cyclin E contribute to the inactivation of CDK2-cycE activity, which is required for G1 arrest (Knoblich *et al*., 1994). A complex promoter that responds to developmental input regulates *Dacapo* gene expression (Meyer *et al*., 2002).

In endocycling nurse cells, Dacapo and cyclin E protein levels oscillate as to permit sequential endoreduplication cycles (Figure 5A; Table 2). Initially, cyclin E triggers Dacapo protein accumulation, which, in turn, inhibits CDK2-cycE activity, allowing correct relicensing of the origins of replication (de Nooij *et al*., 2000). Subsequently, cyclin E levels rise and CDK2-cycE kinase activity becomes high enough to trigger the phosphorylation and destruction of the Dacapo protein, thus allowing endocycle progression (Hong *et al*., 2003).

In vertebrates, CKIs are important to arrest cell cycle progression preceding differentiation and they assist in the promotion of cell differentiation in cooperation with transcription factors. In *Xenopus*, the CKI p27[Xic1] has been shown to be important for cell cycle exit before differentiation of muscle and

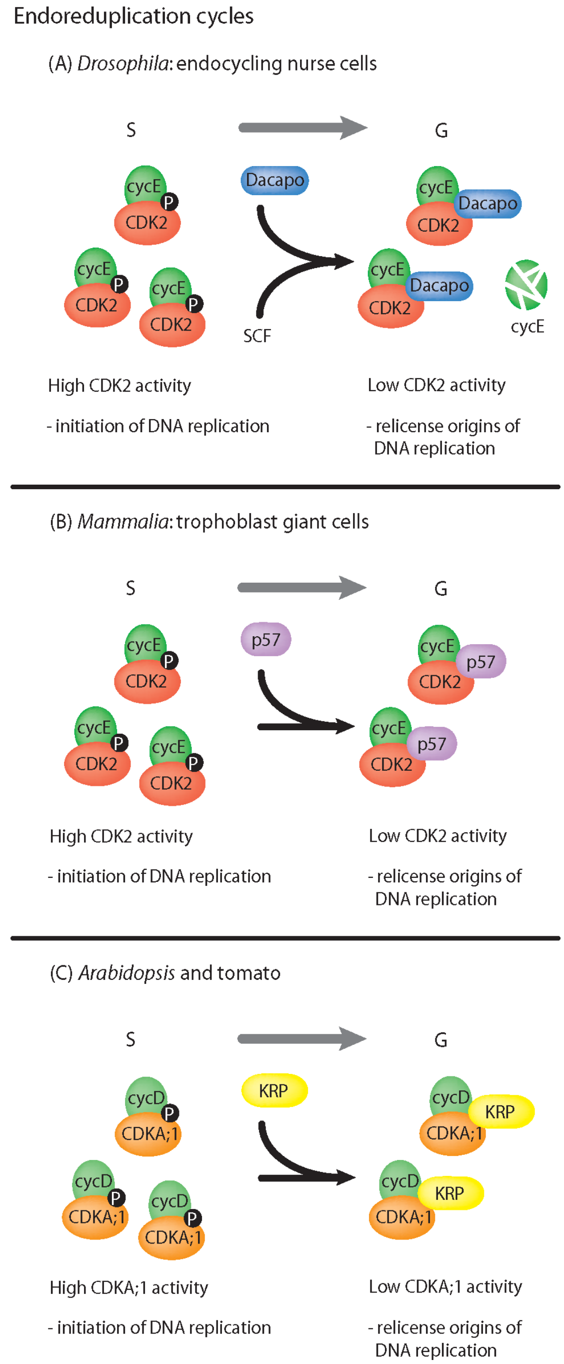

Figure 5 Regulation of CDK activity by CKIs during endoreduplication cycles. (*A*) In *Drosophila* endocycling nurse cells, cyclin E triggers Dacapo accumulation at the end of DNA replication. Dacapo inhibits CDK2-cycE activity, allowing correct relicensing of the origins of DNA replication. Subsequently, cyclin E levels increase again and active CDK2-cycE complexes phosphorylate Dacapo resulting in its destruction and drive a new round of DNA replication. (*B*) In mammalian trophoblast giant cells, p57[Kip2] accumulation after each S phase causes a drop in CDK2-cycE activity, which is required for correct relicensing of the DNA replication origins. (*C*) During differentiation, plant CKIs such as the *Arabidopsis* and tomato KRPs might decrease the CDK activity of endoreduplicating cells in analogy to the *Drosophila* Dacapo and the mammalian p57[Kip2] CKIs. After each S phase, KRPs possibly cause a drop in CDK activity, enabling the relicensing of the origins of DNA replication and, thus, allowing successive endocycles.

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neural cells (Vernon *et al*., 2003; Vernon & Philpott, 2003) (Table 2). Moreover, in the developing myotome, $p27^{Xic1}$ acts together with MyoD to promote myogenic differentiation (Vernon & Philpott, 2003). In cells destined to become primary neurons, $p27^{Xic1}$ stabilizes the transcription factor neurogenin, required for primary neurone differentiation (Vernon *et al*., 2003) (Table 2).

In mammals, the Ink4 and Cip/Kip proteins are involved in several mechanisms that control cell cycle arrest and terminal differentiation (Table 2). For instance, the Ink4 protein $p16^{Ink4a}$ is up-regulated together with the Cip/Kip inhibitor $p21^{Cip1}$ in senescent cells (Tahara *et al*., 1995; Palmero *et al*., 1997) and has been suggested to be actively involved in establishing cellular senescence (Serrano, 1997). During terminal differentiation of late-stage B cells to plasma cells, the Ink4 protein $p18^{Ink4c}$ plays an important role in regulating cell cycle arrest through inhibition of CDK6 (Morse *et al*., 1997). Furthermore, the $p18^{Ink4c}$ protein is highly induced in terminally differentiating myotubes to inhibit CDK4 and CDK6 (Phelps *et al*., 1998). In addition, $p21^{Cip1}$ and the transcription factor MyoD link cell proliferation with differentiation in myogenic tissue culture systems. Upon serum withdrawal, MyoD can transcriptionally up-regulate *$p21^{Cip1}$* expression, causing cell cycle arrest and muscle differentiation (Halevy *et al*., 1995). However, mice that lack $p21^{Cip1}$ show normal myotube formation without developmental defects (Deng *et al*., 1995). Nevertheless, deletion of both *$p21^{Cip1}$* and *$p57^{Kip2}$* genes results in mice with defective muscle differentiation, demonstrating that $p21^{Cip1}$ and $p57^{Kip2}$ cooperate to control development of mouse skeletal muscle (Zhang *et al*., 1999). Studies on mice lacking $p27^{Kip1}$ have uncovered a prominent role in the decision to withdraw from the cell cycle (Table 2). *$p27^{Kip1}$*-deficient mice are significantly larger than control mice because of an increase in the number of cells, suggesting that the absence of $p27^{Kip1}$ might allow continued cell proliferation in the presence of antimitogenic signals (Fero *et al*., 1996; Kiyokawa *et al*., 1996; Nakayama *et al*., 1996).

When cells differentiate during development, they express *CKI* genes to arrest cell cycle progression. However, terminal differentiation of some cell types is not associated with cell cycle exit, but rather with endoreduplication. In mammalian trophoblasts, ectopic expression of *$p57^{Kip2}$* promotes giant cell differentiation, while expression of a stable mutant form of the protein blocks endoreduplication (Hattori *et al*., 2000). In endocycling trophoblasts, $p57^{Kip2}$ accumulates at the end of each S phase and is destroyed prior to the subsequent S phase (Hattori *et al*., 2000) (Figure 5B). $p57^{Kip2}$ accumulation causes a drop in CDK activity after each S phase, which is required for correct re-initiation of origins of replication (Table 2). In *Drosophila*, the Dacapo protein also oscillates in endocycling nurse cells (Hong *et al*., 2003), indicating that oscillation of Cip/Kip proteins may be a common feature of endocycles in diverse organisms.

Plants

In plants, exit from the mitotic cell cycle and initiation of differentiation frequently coincide with the onset of endoreduplication. The endoreduplication cycle shares several characteristics with the mitotic cell cycle. In particular, the endoreduplication cycle appears to be under control of the same CDK/cyclin complexes. However, both cycles are mutually exclusive and higher eukaryotes have developed strategies, ensuring that endoreduplication is inhibited during mitosis and *vice versa* (Edgar & Orr-Weaver, 2001; Larkins *et al*., 2001).

In plants, CKIs have been shown to play important roles in the switch between cell proliferation and cell differentiation during development. Ectopic expression of *CKI* genes results in plants with modified morphogenesis and reduced endoreduplication in older leaves (Wang *et al*., 1998; De Veylder *et al*., 2001; Jasinski *et al*., 2002b; Zhou *et al*., 2002a). Recent evidence demonstrated that the observed effects of KRP1 and KRP2 of *Arabidopsis* on the developmental process depend on the level of *KRP* overexpression (Verkest *et al*., 2005; Weinl *et al*., 2005). Specific misexpression of *KRP1* in *Arabidopsis* trichomes with the *GLABRA2* promoter reduces cell size and endoreduplication levels. However, the trichome-neighboring cells in these *KRP1*-misexpressing plants are enlarged and show higher endoreduplication. These different phenotypes are due to a lower concentration of KRP1 in the trichome-neighboring cells and indicate that KRP1 works in a dose-dependent manner (Weinl *et al*., 2005) (Table 2). In weak *KRP2*-overexpressing lines (*$KRP2^{OE}$*), KRP2 preferentially targets mitotic cell cycle-specific

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CDKA;1 kinase complexes, whereas the endocycle-specific CDKA;1 kinase complexes are unaffected, resulting in an increase in the DNA ploidy levels (Verkest *et al*., 2005) (Table 2). However, in strong $KRP2^{OE}$ lines, both mitotic cell cycle-specific and endoreduplication cycle-specific CDKA;1 kinase complexes are inhibited, resulting in an overall inhibition of the cell cycle (Wang *et al*., 1998; De Veylder *et al*., 2001; Jasinski *et al*., 2002b; Zhou *et al*., 2002a; Verkest *et al*., 2005). Recently, two CKIs (KRP1 and KRP2) have been identified in tomato (*Lycopersicon esculentum*) that show sequence similarity with the *Arabidopsis* KRPs in their C-terminal domain. LeKRP1 has been shown to inhibit CDK activity in endoreduplicating tissue, suggesting a role in controlling the transition from mitotic cell cycle to endoreduplication cycle and in regulating CDK activity during successive endocycles (Bisbis *et al*., 2006) (Table 2). Plant CKIs probably function in decreasing CDK activity of endoreduplicating cells in accordance with the *Drosophila* Dacapo and the mammalian $p57^{Kip2}$ inhibitors (Figure 5C). These CKIs cause a drop in CDK activity after each S phase and this down-regulation is required to relicense origins to allow successive endocycles (Hattori *et al*., 2000; Hong *et al*., 2003).

Contrary to animal CKIs, plant CKIs can function in a non-cell-autonomous manner (Weinl *et al*., 2005). The finding that KRP1 can move between cells adds another level of complexity to plant development and suggests that the plant KRPs can operate as a link between decisions on the cellular and on the supracellular level. For instance, when starting from the leaf tip, epidermal cells enter the endocycle progressively (Melaragno *et al*., 1993; Dengler & Kang, 2001; Beemster *et al*., 2005) and CKIs could help to spread the entry into the endoreduplication cycle. Similarly, in *C. elegans*, a non-cell-autonomous function was suggested for the CKI cki-1 (Hong *et al*., 1998). Although it remains unknown how CKIs act in a non-cell-autonomous manner, it seems an evolutionarily conserved mechanism that provides an additional level of cell cycle control.

ADDITIONAL FUNCTIONS OF CKIs

In eukaryotes, CKIs function not only as inhibitors of cell cycle progression or as regulators of cell cycle exit preceding differentiation, but also participate in controlling other pathways.

Yeast

An additional function for the budding yeast CKI $p40^{Sic1}$ has been suggested as assembly factor of Cdc28/Clb5–6 complexes. In exponentially growing cells, mutation of the Ser-201 phosphorylation site on $p40^{Sic1}$ resulted in larger cells with a significant increase in average protein content (Coccetti *et al*., 2004). This phenotype with larger cells resembles that of $p40^{Sic1}$ deletion mutants (Lengronne & Schwob, 2002) and is unexpected, because deletion of a CKI should increase cell division rate and result in smaller cells. Nevertheless, the larger size of the cells might be explained if $p40^{Sic1}$ has a function in promoting Cdc28/Clb assembly, like the mammalian CKIs $p21^{Cip1}$ and $p27^{Kip1}$ (LaBaer *et al*., 1997; Cheng *et al*., 1999). By mutating Ser-201 in $p40^{Sic1}$, the ability to assemble Cdc28/Clb complexes is diminished, resulting in lower kinase activity and larger cells. Alternatively, the phenotype with larger cells can also be explained if $p40^{Sic1}$ plays a role in inhibition of cell growth. The CKI Far1 also has a function that is distinct from its role as cell cycle inhibitor. The cytoplasmic form of Far1 regulates cell orientation toward the mating partner (Gulli & Peter, 2001).

Animals

Besides its essential role in cell proliferation and differentiation, the nematode cki-1 regulates morphogenesis, cell migration, and cell death (Fukuyama *et al*., 2003). For body morphogenesis and organogenesis, cell divisions and migration must be tightly coordinated. Similarly, a function in regulation of cell migration has been suggested for the mammalian Cip/Kip inhibitors (Besson *et al*., 2004). Furthermore, cki-1 might suppress programmed cell death (Fukuyama *et al*., 2003), which has also been observed for the mammalian Cip/Kip inhibitors (Suzuki *et al*., 1998, 1999; Asada *et al*., 1999). However, the precise regulatory mechanisms of cki-1 in these processes remain to be elucidated.

Cip/Kip proteins in mammals also participate in monitoring other pathways. First, Cip/Kip proteins act during cell proliferation as assembly factors in the cytoplasm, where they enhance binding of cyclin D to CDK4 (Cheng *et al*., 1999). Futhermore, cytoplasmic Cip/Kip proteins also target D-type complexes that do not possess signal motifs for nuclear localization to the nucleus (LaBaer *et al*., 1997). Additionally, $p21^{Cip1}$ has been shown to promote nuclear accumulation of cycD1

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by binding to its phosphorylated form to prevent its CRM1 association and nuclear export (Alt *et al*., 2002).

Second, Cip/Kip proteins regulate apoptosis by several mechanisms. p21^{Cip1} protects cells from p53-mediated apoptosis (Gorospe *et al*., 1997) and *p21^{Cip1}*-expressing cells produce anti-apoptotic proteins that might influence the survival of adjacent cells through a paracrine effect (Chang *et al*., 2000). Moreover, p21^{Cip1} becomes cytoplasmic during monocytic differentiation and inhibits the stress-activated protein kinases and apoptosis signal-regulating kinase 1. Hereby, p21^{Cip1} blocks the stress-mediated MAPK cascade and prevents apoptosis (Asada *et al*., 1999). Finally, p21^{Cip1} interacts on mitochondria with procaspase-3 to inhibit caspase-3 activation and to resist against Fas-mediated cell death (Suzuki *et al*., 1998, 1999).

Third, Cip/Kip proteins function as regulators of cell anchorage and migration. For proliferation of untransformed tissue cells, anchorage to the extracellular matrix of neighboring cells is a requirement (Ruoslahti & Reed, 1994) and results in up-regulation of CDK2-cycE and down-regulation of p21^{Cip1} and p27^{Kip1} (Fang *et al*., 1996; Strömblad *et al*., 1996; Zhu *et al*., 1996). Integrin-regulated proteasomal degradation of p21^{Cip1} might contribute to the control of cell proliferation by anchorage. An integrin-to-Cdc42/Rac signaling pathway has been identified that mediates the anchorage-induced proteolysis of p21^{Cip1} (Bao *et al*., 2002). Furthermore, cytoplasmic p27^{Kip1} is involved in promoting cell migration through inhibition of the Rho pathway (Besson *et al*., 2004).

Finally, Cip/Kip proteins work as transcriptional cofactors. p21^{Cip1} can down-regulate E2F transcription in a Rb-independent fashion *in vitro* (Delavaine & La Thangue, 1999). In addition, p21^{Cip1} can inhibit transcriptional activation of signal transducer and activator of transcription 3 (Coqueret & Gascan, 2000). Moreover, direct binding of p21^{Cip1} and c-Myc has been demonstrated (Kitaura *et al*., 2000). The transcription factor c-Myc plays an important role in the transition from quiescence to proliferation and binding of c-Myc to p21^{Cip1} can activate DNA replication by inactivation of p21^{Cip1} and, *vice versa*, binding of p21^{Cip1} to c-Myc can repress the transcriptional activity of c-Myc. The balance between c-Myc and p21^{Cip1} might determine cellular processes, such as cell proliferation, differentiation, and apoptosis.

Plants

Knowledge on additional functions of CKIs in plants has just started to emerge. In *Arabidopsis* trichomes, misexpression of *KRP1* causes programmed cell death at later stages of development (Schnittger *et al*., 2003). Similarly in animals, p21^{Cip1} and p27^{Kip1} are considered as regulators of apoptosis, but they enhance cell survival (Suzuki *et al*., 1998; 1999; Asada *et al*., 1999).

CONCLUSION

In yeast, animals, and plants, CKIs play an essential role in orchestrating cell proliferation and differentiation and are involved in other processes, such as apoptosis, cell migration, and transcriptional regulation. During mitotic cell cycle progression, CKIs inhibit CDK activity to keep cells in the G1 phase in response to environmental and developmental cues. The CKIs p25^{Rum1} of fission yeast and p40^{Sic1} of budding yeast inhibit Cdc2 and Cdc28 activity, respectively, to prevent G1-S transition until the cell size is sufficient to start DNA replication. In *C. elegans*, cki-1 maintains progenitor cells in G1 phase prior to later proliferation. In mitotically dividing cells, the CKIs p40^{Sic1} of budding yeast and Roughex of *Drosophila* and the mammalian CKIs p21^{Cip1} and p27^{Kip1}, assist in inactivation of the CDK activity required for mitotic exit and establishment of a G1 phase. During mitotic cell cycles, the *Xenopus* CKIs p27^{Xic1} and p28^{Kix1} and the mammalian CKIs of the Cip/Kip family inhibit CDK4/6-cycD, CDK2-cycE and CDK2-cycA complexes, while the mammalian CKIs of the Ink4 family bind CDK4 and CDK6 to prevent the G1-S transition. CKIs of *Arabidopsis*, tobacco and maize arrest mitotic cell cycles by inhibiting CDK kinase activity.

Additionally, CKIs decide on cell cycle arrest and link cell proliferation with differentiation. The CKIs p25^{Rum1} of fission yeast and Far1 of budding yeast are important regulators of cell cycle exit in G1 phase and of differentiation in response to external signals, such as nutrient starvation or pheromone signaling. During development, cki-1 of *C. elegans* regulates normal embryonic cell cycle exit before differentiation. The *Drosophila* CKI Dacapo mediates cell cycle arrest in G1 prior to differentiation and inhibits CDK activity prior to each S phase in endoreduplicating cells. The vertebrate CKIs, such as p27^{Xic1} and p28^{Kix1}

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of *Xenopus* and the mammalian Ink4 and Cip/Kip proteins drive cell cycle exit and work together with transcription factors to promote terminal differentiation. Furthermore, $p57^{Kip2}$ is involved in regulating CDK activity in endocycling cells. In differentiating *Arabidopsis* cells, KRP1 and KRP2 are essential in switching from a mitotic to an endoreduplicating cell cycle mode and can assist in terminating both mitotic and endoreduplicating cycles during development. In addition, a role has been suggested for the *Arabidopsis* and tomato KRPs in regulating CDK activity during successive endocycles.

Thus, CKIs in yeast, animals, and plants participate in conserved eukaryotic mechanisms of cell proliferation and cell differentiation. However, functions of CKIs are adapted to the environment and developmental stage of the cells and to the mechanisms that specifically occur in yeast, animals or plants.

Although functions and regulation of CKIs become well characterized, there is still a lot of interesting research to be done. Increasing knowledge of the differential functions of CKIs in eukaryotes will help us to fully understand their roles during cell cycle progression and in linking cell proliferation, differentiation, and other cellular and supracellular processes.

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