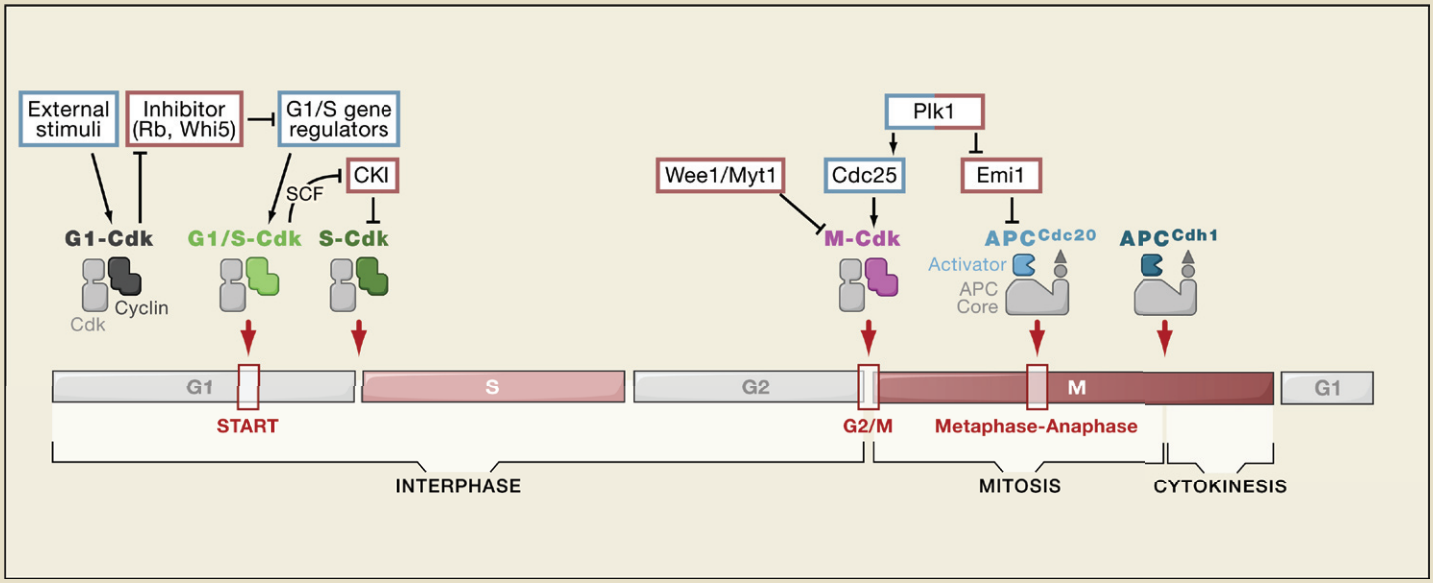
SnapShot: Cell-Cycle Regulators II

David O. Morgan
University of California, San Francisco, CA 94143, USA

Cell



	Function	*S. cerevisiae* (Budding Yeast)	*S. pombe* (Fission Yeast)	*D. melanogaster* (Fruit Fly)	*X. laevis* (Clawed Toad)	*H. sapiens* (Human)
Cdk-inhibitory kinases	Phosphorylate Cdk in active site, blocking activity	**Swe1**	**Wee1, Mik1**	**Dwee1, Dmyt1**	**Wee1, Myt1**	**Wee1, Myt1**
Cdk-activating phosphatases	Dephosphorylate inhibitory phosphorylation of Cdk subunit	**Mih1**	**Cdc25**	**String, Twine**	**Cdc25A, B, C**	**Cdc25A, B, C**
Cdk inhibitor proteins (CKIs) (selected)	Sic1 class: inhibits S and M phase Cdks	**Sic1**	**Rum1**	**Roughex** (Rux)		
	Cip/Kip class: inhibits G1, S, M phase Cdks and activates G1 Cdks			**Dacapo** (Dap)	**Xic1** (Kix1)	**p21** (Cip1, Waf1), **p27** (Kip1), **p57** (Kip2)
	INK4 class: inhibits G1 Cdks					**p15^{Ink4b}, p16^{Ink4a}, p18^{Ink4c}, p19^{Ink4d}**
APC inhibitors (selected)	Bind activating subunit, often as pseudosubstrates	**Acm1** binds Cdh1	**Mes1** binds Cdc20 in meiosis	**Rca1** binds Cdh1	**Xerp1** (Emi2) binds Cdc20 in meiosis	**Emi1** binds Cdc20 and Cdh1
SCF (Skp1-Cullin-F box) ubiquitin ligase F-box subunits (selected)	Recruit indicated substrates to SCF ligase for ubiquitination	**Cdc4** recruits Sic1, Far1, Cdc6				**Fbw7** (Cdc4, Ago) recruits cyclin E
						β-**TrCP1** recruits Cdc25A, Wee1, Emi1
		Grr1 recruits Cln1, 2				**Skp2** recruits E2F-1, p27
G1/S gene control		Transcription factors: Sequence-specific DNA-binding proteins at G1/S gene promoters				
		SBF (Swi6 + Swi4): activator		**dE2F1**: activator		**E2F-1, 2, 3**: activators
		MBF (Swi6 + Mbp1): regulator		**dE2F2**: repressor		**E2F4, 5**: repressors
		Cdk-dependent inhibitors: Inhibit activators or assist repressors; inhibited by G1-Cdk				
		Whi5		**dRBF1, dRBF2**		**pRB, p107, p130**

See online version for legend and references.

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The core components of the cell-cycle control system are governed by numerous additional regulators, which ensure that cyclin-dependent kinase (Cdk) and anaphase-promoting complex (APC) activities are robustly and rapidly activated in the correct order and at the appropriate cell-cycle stage. Cyclin-Cdk activities are controlled by phosphorylation at inhibitory sites on the Cdk subunit, association with Cdk-inhibitory proteins (CKIs), transcriptional control of cyclins and other regulators, and the ubiquitin-dependent proteolysis of cyclins and CKIs. APC activity is fine-tuned by inhibitory proteins that restrain its function outside mitosis.

A multisubunit ubiquitin ligase called SCF contributes to early cell-cycle control by triggering the ubiquitination and destruction of some CKIs and G1/S cyclins. The SCF core (containing three subunits, not listed here) interacts with numerous F-box proteins that recruit specific substrates for ubiquitination. Typically, SCF targets must be phosphorylated by Cdks or other kinases to allow their recognition by F-box subunits of SCF.

Progression through the cell cycle depends in part on transcriptional regulators, including the particularly well-understood regulators of G1/S gene expression at the beginning of the cycle. Prior to cell-cycle entry, these regulators interact with inhibitor proteins, blocking the activation of G1/S gene expression and, in some cases, actively repressing it. G1-Cdks phosphorylate and thereby inactivate these inhibitors, unleashing G1/S gene expression.

Although the details vary among different species, the general scheme of eukaryotic cell-cycle control can be summarized as follows. In response to the appropriate extracellular signals or cell size, G1-Cdks trigger G1/S gene expression, leading to expression of G1/S and S cyclins and other components required for S phase events. G1/S-Cdk activation helps promote S-Cdk activation, at least in some cases, by phosphorylating CKIs and thereby targeting them to SCF for ubiquitination. G1/S- and S-Cdks then collaborate to initiate chromosome duplication and duplication of the spindle poles. M cyclins rise during S phase or thereafter, but M-Cdk complexes are initially restrained in many species by inhibitory phosphorylation by Wee1-related inhibitory kinases. Dephosphorylation by Cdc25-related phosphatases then triggers M-Cdk activation, resulting in mitotic spindle assembly and other preparations for chromosome segregation. When the chromosomes are aligned on the spindle, activation of APC^{Cdc20} initiates sister-chromatid separation and Cdk inactivation, leading to dephosphorylation of Cdk substrates and the completion of mitosis and cytokinesis. Declining Cdk activity results in the activation of APC^{Cdh1}, which continues to suppress cyclin levels until it is inactivated by Cdks at the beginning of the next cell cycle.

Multiple additional regulators, not listed here, collaborate with Cdks and the APC to govern cell-cycle events. In mitosis, for example, the protein kinases Plk1, Aurora A, and Aurora B contribute in multiple ways to the control of mitotic spindle and chromosome function. Plk1 stimulates mitotic progression in part by promoting Cdc25 activation and inhibiting the APC inhibitor Emi1. Mitotic progression also depends on a regulatory system called the spindle assembly checkpoint, which suppresses APC^{Cdc20} activity until all sister chromatid pairs are correctly attached to both spindle poles. APC^{Cdc20} activity is directly inhibited by checkpoint components, notably Mad2 and Mad3, which bind and inhibit Cdc20 before metaphase but are released from Cdc20 when chromosome alignment occurs.

Abbreviations

Cdk, cyclin-dependent kinase; CKI, Cdk-inhibitory protein; APC, anaphase-promoting complex or cyclosome; SCF, Skp1-Cullin-F box complex.

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