LGN5809 - Genética Molecular

SISTEMA DE CONTROLE DO CICLO CELULAR

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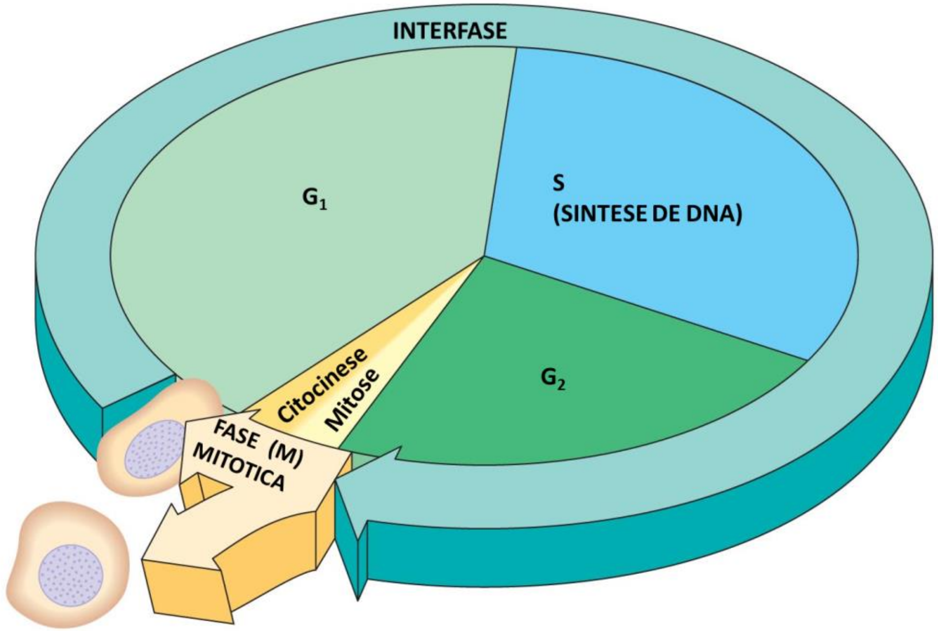
SUMÁRIO

- *Overview* do ciclo celular;
- Controle do ciclo celular em procariotos;
- Controle do ciclo celular em eucariotos;
- Papel das Ciclinas-CDKs na sinalização do ciclo celular;
- Controle do ciclo celular senescência e câncer;
- Ciclinas – CDKs em plantas?
- Próxima aula

DEFINIÇÃO

Ciclo celular um conjunto de processos que sofre uma célula entre duas divisões celulares. O ciclo celular consiste na intérfase e na fase mitótica, que inclui a mitose e a divisão celular (citocinese)


INTERFASE
G1
S
(SINTESE DE DNA)
G2
Citocinese
Mitose
FASE (M)
MITOTICA

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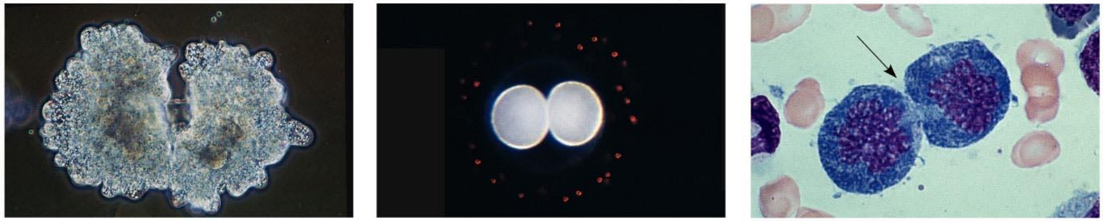
A FUNÇÃO E CONTROLE DO CICLO CELULAR DEPENDE DO ORGANISMO!!!

✓ **PROCARIOTOS:**

- Fissão binária.



(a) (b) (c)

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✓ **EUCARIOTOS:**

✓ **MITOSE:**

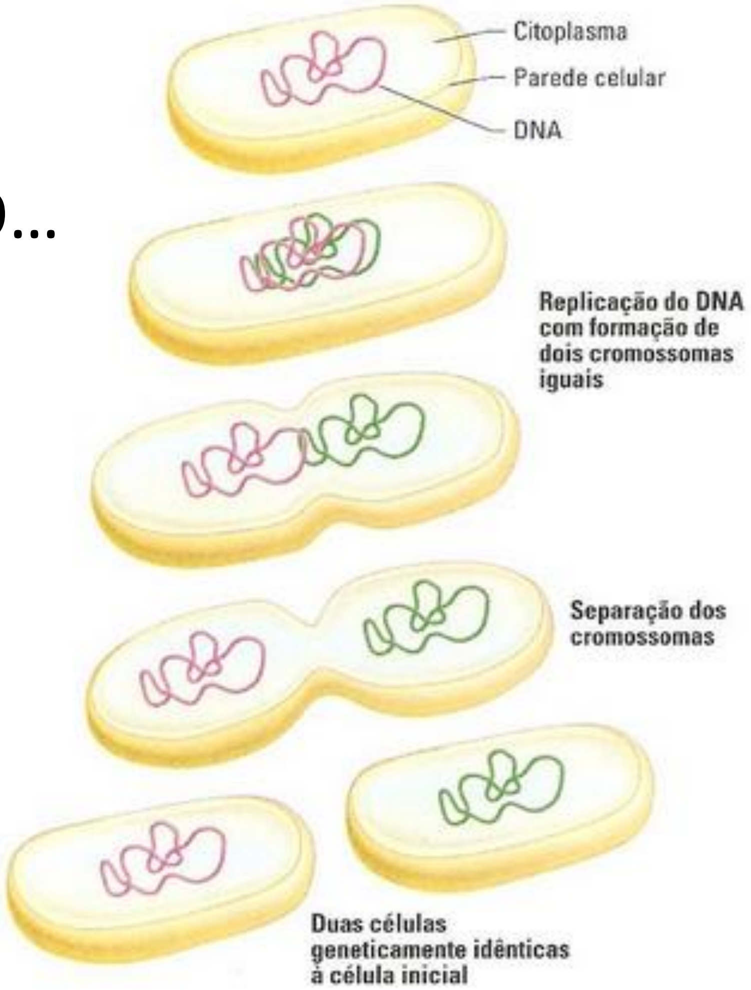
- Crescimento, desenvolvimento e reparo;
- Reprodução asssexuada (gera duas células idênticas);
- Ocorre nas células somáticas.

✓ **MEIOSE:**

- Reprodução sexuada;
- Ocorre em células reprodutivas;
- Origina gametas.

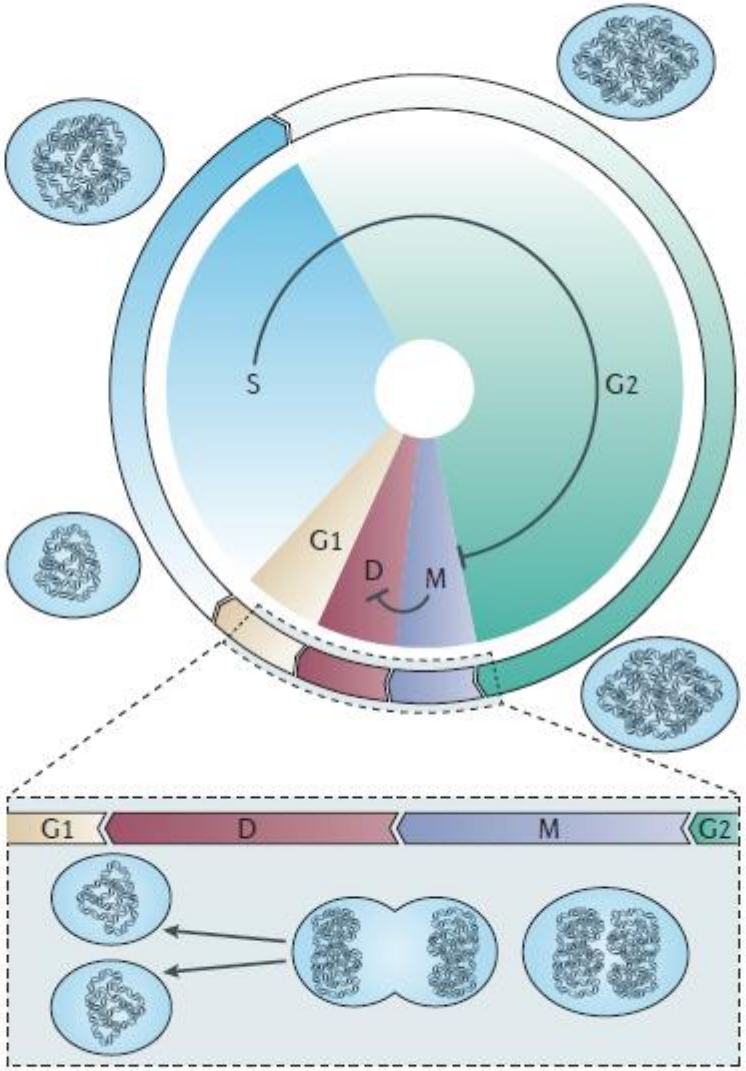
CICLO CELULAR EM PROCARIOTOS

Modelo clonal CLÁSSICO…
fissão binária!


Citoplasma
Parede celular
DNA
Replicação do DNA com formação de dois cromossomas iguais
Separação dos cromossomas
Duas células geneticamente idênticas à célula inicial

COMPARAÇÃO DOS CICLOS CELULARES ENTRE OS DOMINIOS

Evento	Procariota	Eucariota
Crescimento da massa celular (pré-replicativo)	Período B (G1)	Fases G1 ou gap 1
Replicação do cromossomo (replicativo)	Período C (S)	Fases S (síntese de DNA)
Separação dos cromossomos (pós-replicativo)	Período D (G2,M)	Fase G2 (gap 2) Mitose ou fase M
Separação das células (pós-replicativo)	Período D (citocinese)	Citocinese


S
G2
G1
D
M
G1
D
M
G2

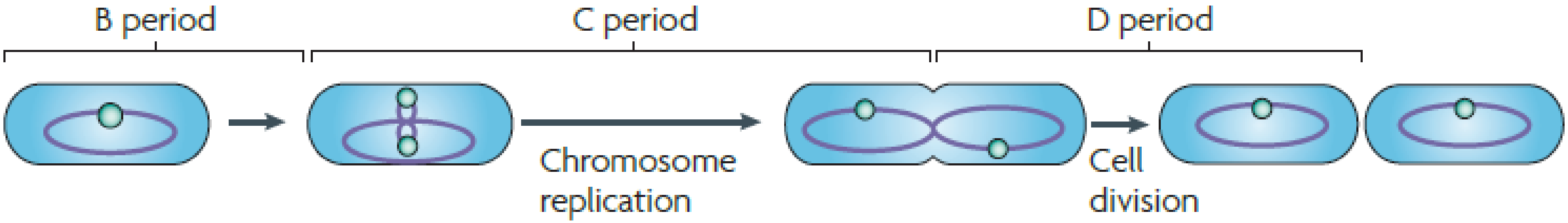
Arquéia ciclo celular com eventos parecido com de eucariotos

doi:10.1038/nrmicro3077

EM BACTÉRIAS…

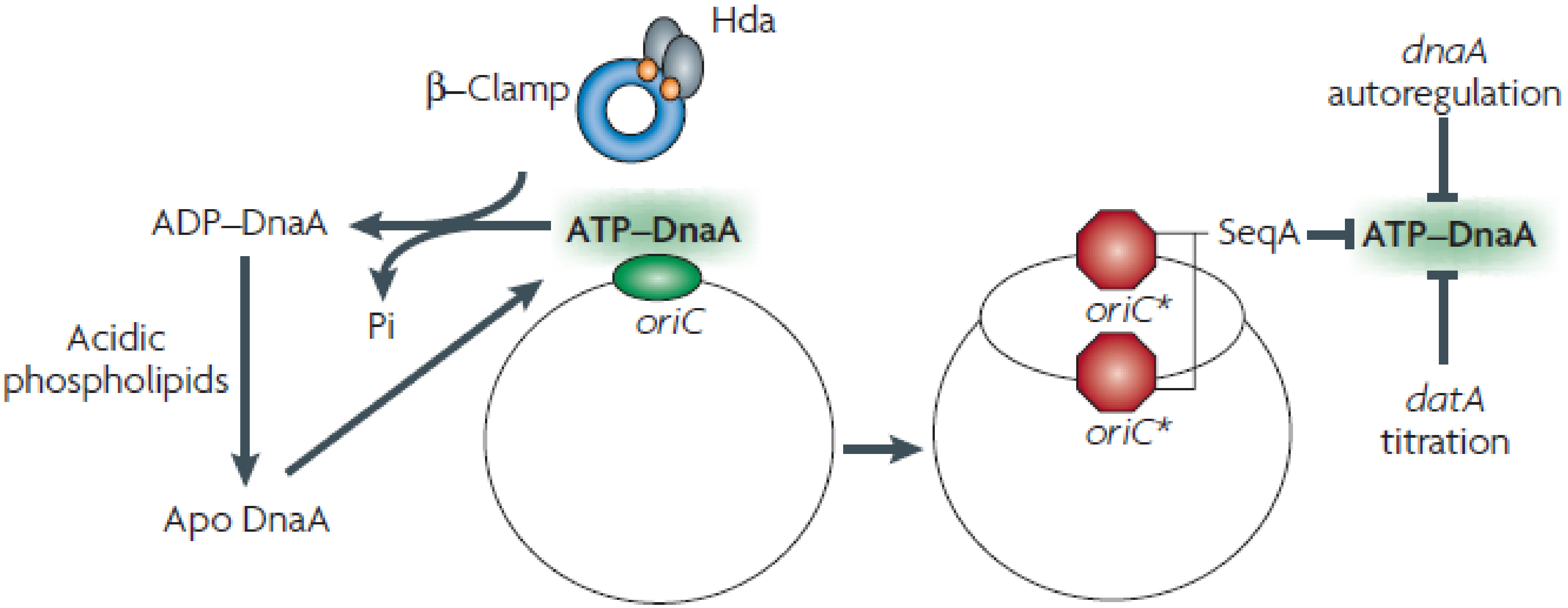
Período C e D – tempo constante!

Período B – Tempo altamente determinado por fatores nutricionais!


B period
C period
D period
Chromosome replication
Cell division

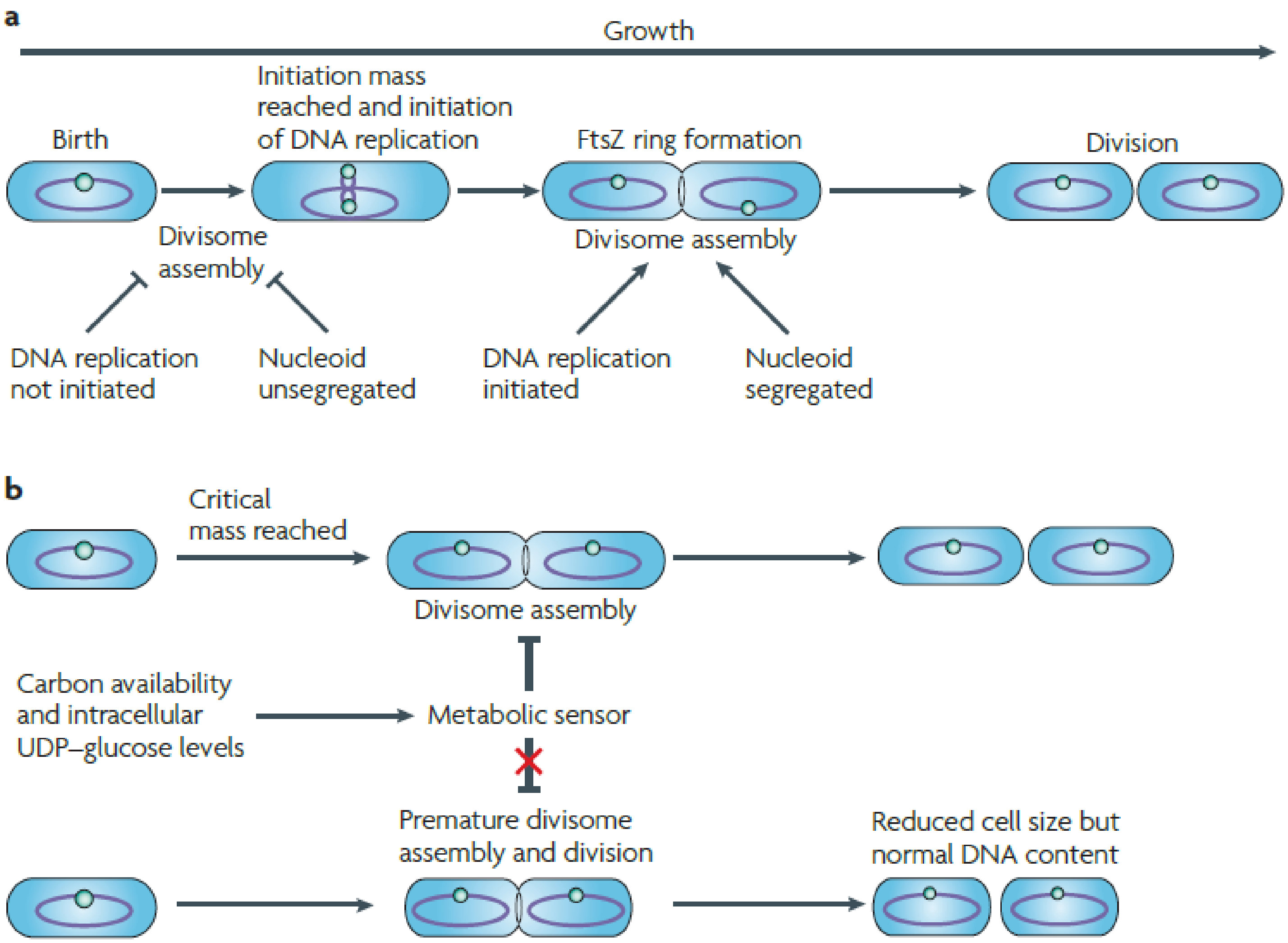
doi:10.1038/nrmicro2202

CONTROLE DA REPLICAÇÃO …*E. coli* ORGANISMO MODELO


Hda
β–Clamp
ADP–DnaA
ATP–DnaA
Pi
Acidic phospholipids
Apo DnaA
oriC
oriC*
oriC*
SeqA
ATP–DnaA
dnaA autoregulation
datA titration

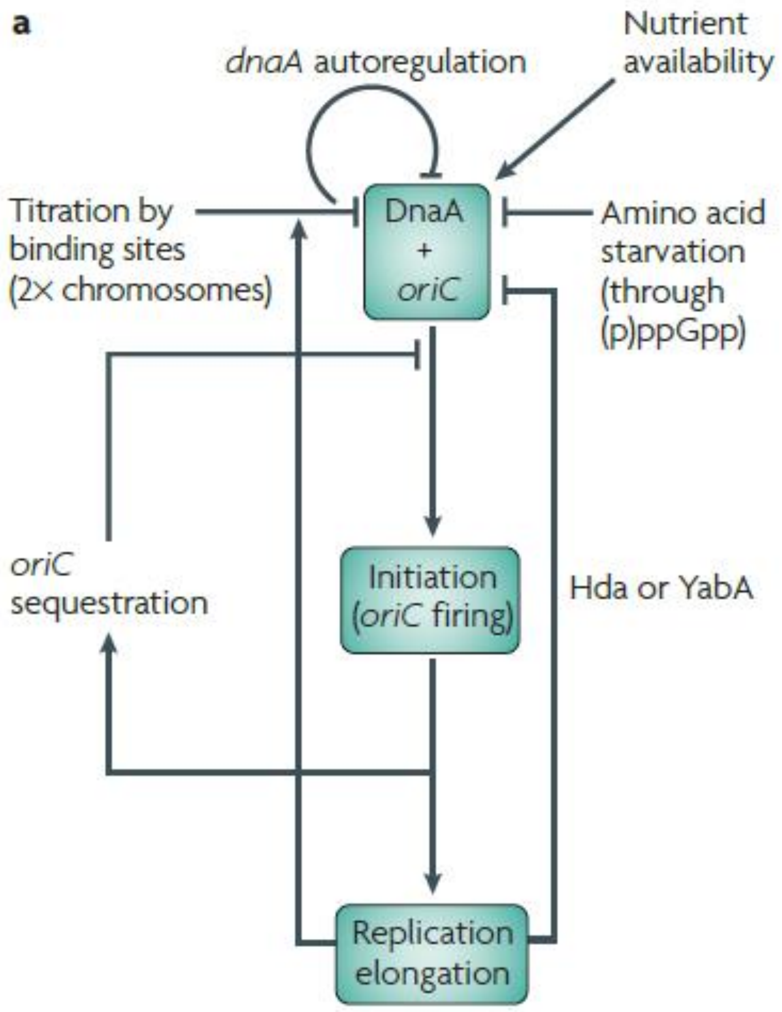
doi:10.1038/nrmicro1640

VÁRIOS FATORES INFLUENCIANDO O CICLO CELULAR …


a
Growth
Birth
Initiation mass reached and initiation of DNA replication
FtsZ ring formation
Division
Divisome assembly
Divisome assembly
DNA replication not initiated
Nucleoid unsegregated
DNA replication initiated
Nucleoid segregated
b
Critical mass reached
Divisome assembly
Carbon availability and intracellular UDP–glucose levels
Metabolic sensor
Premature divisome assembly and division
Reduced cell size but normal DNA content

doi:10.1038/nrmicro2202

A INTERAÇÃO ENTRE INICIADORES DE REPLICAÇÃO E *oric*


a
dnaA autoregulation
Nutrient availability
Titration by binding sites (2× chromosomes)
DnaA + *oriC*
Amino acid starvation (through (p)ppGpp)
oriC sequestration
Initiation (*oriC* firing)
Hda or YabA
Replication elongation

Vários fatores influenciam o controle da replicação...

Destaque para a (p)ppGpp)

doi:10.1038/nrmicro2202

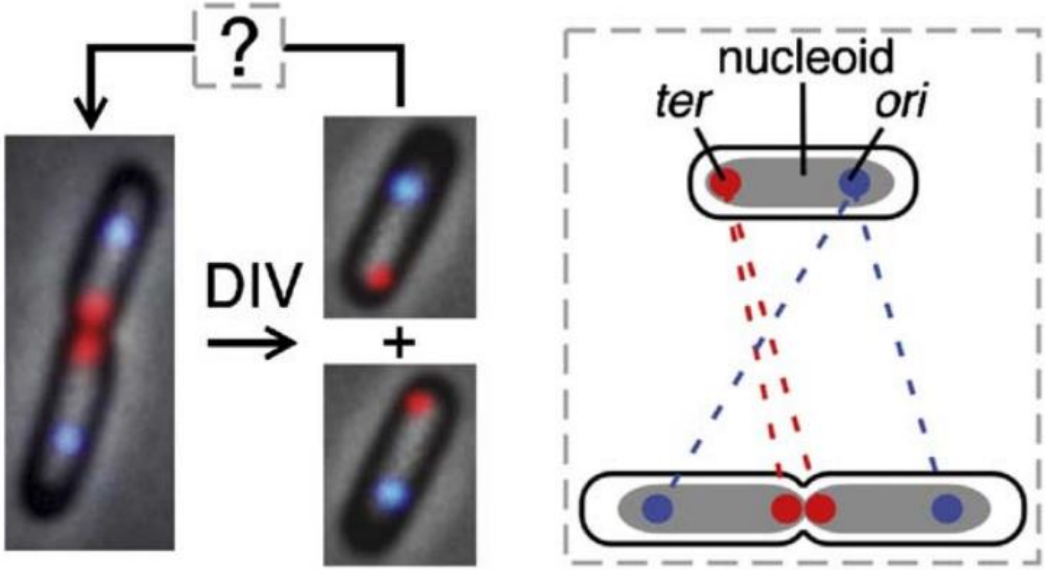
Cell, Vol. 121, 899–911, June 17, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.cell.2005.04.013

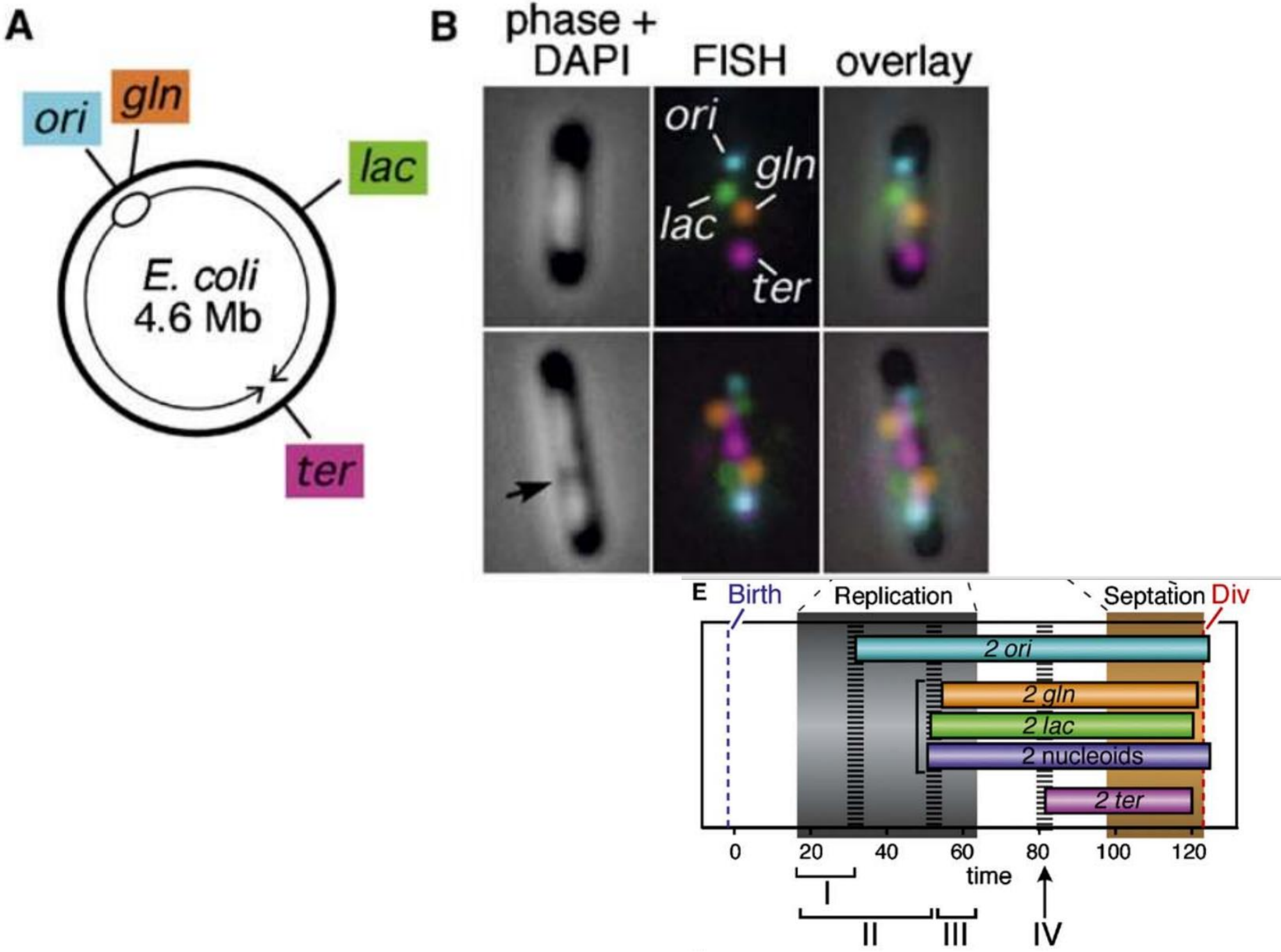
Chromosome and Replisome Dynamics in *E. coli*: Loss of Sister Cohesion Triggers Global Chromosome Movement and Mediates Chromosome Segregation

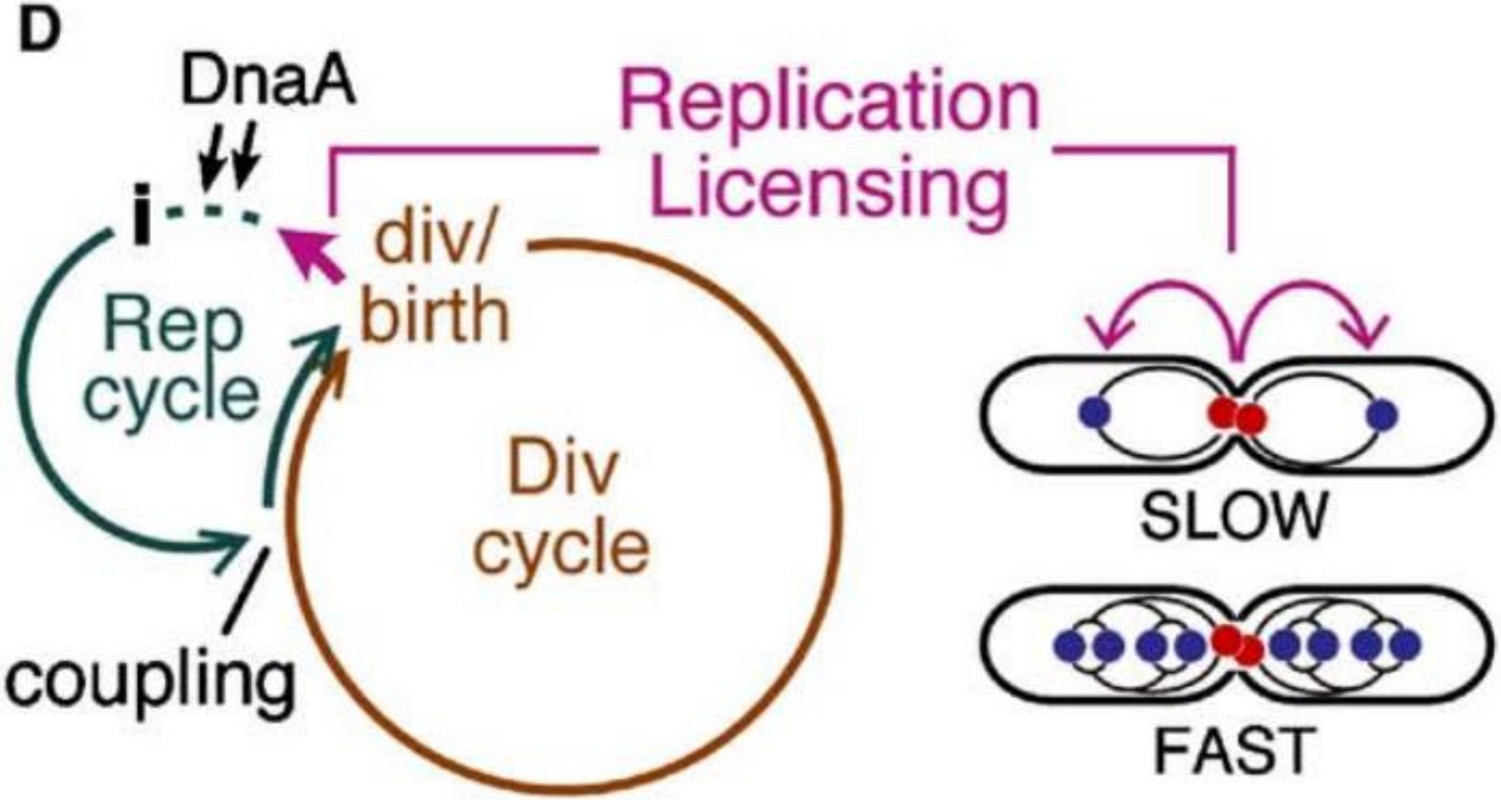
David Bates* and Nancy Kleckner
Department of Molecular and Cellular Biology
Harvard University
Cambridge, Massachusetts 02138

Summary

Chromosome and replisome dynamics were examined in synchronized *E. coli* cells undergoing a eukaryotic-like cell cycle. Sister chromosomes remain tightly colocalized for much of S phase and then separate, in a single coordinate transition. Origin and terminus regions behave differently, as functionally independent domains. During separation, sister loci move far apart and the nucleoid becomes bilobed. Origins and terminus regions also move. We infer that sisters are initially linked and that loss of cohesion triggers global chromosome reorganization. This reorganization creates the 2-fold symmetric, *ter*-in/*ori*-out conformation which, for *E. coli*, comprises sister segregation. Analogies with eukaryotic prometaphase suggest that this could be a primordial segregation mechanism to which microtubule-based processes were later added. We see no long-lived replication "factory"; replication initiation timing does not covary with cell mass, and we identify changes in nucleoid position and state that are tightly linked to cell division. We propose that cell division licenses the next round of replication initiation via these changes.




A
ori
gln
lac
E. coli
4.6 Mb
ter
B
phase + DAPI
FISH
overlay
ori
gln
lac
ter
E
Birth
Replication
Septation
Div
2 ori
2 gln
2 lac
2 nucleoids
2 ter
0
20
40
60
80
100
120
time
I
II
III
IV


D
DnaA
i
Replication
Licensing
div/
birth
Rep
cycle
Div
cycle
coupling
SLOW
FAST

Começa a separar antes de terminar a replicação…FstZ controlado pela presença de DnaA e outras proteínas

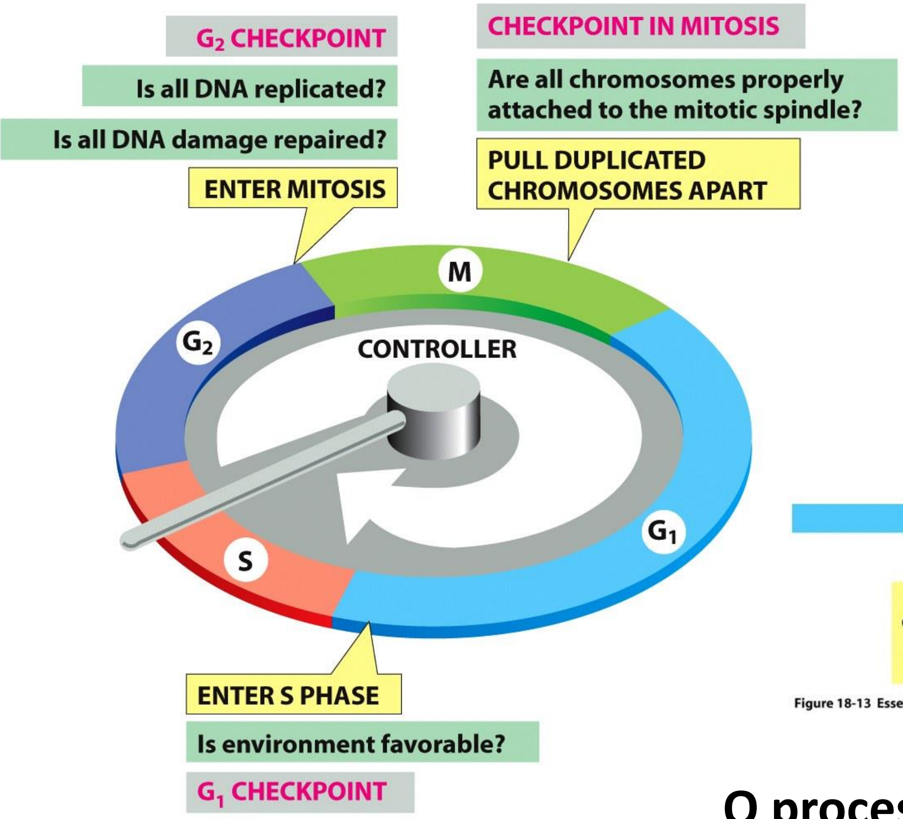
TIPOS DE CICLOS CELULARES EM PROCARIOTOS

- ✓ maioria fissão binária;
- ✓ alguns utilizam fissão múltipla, brotamento ou fissão assimétrica

Arquéia possuem características mistas de bactérias e eucariotos em seu ciclo

E EM EUCARIOTOS O CONTROLE É O MESMO??

A DECISÃO ERRÔNEA DA MULTIPLICAÇÃO TRÁS CONSEQUÊNCIAS DRÁSTICAS…


G_2 CHECKPOINT
Is all DNA replicated?
Is all DNA damage repaired?
ENTER MITOSIS
CHECKPOINT IN MITOSIS
Are all chromosomes properly attached to the mitotic spindle?
PULL DUPLICATED CHROMOSOMES APART
M
G_2
CONTROLLER
S
G_1
ENTER S PHASE
Is environment favorable?
G_1 CHECKPOINT

3 PONTOS DE VERIFICAÇÃO

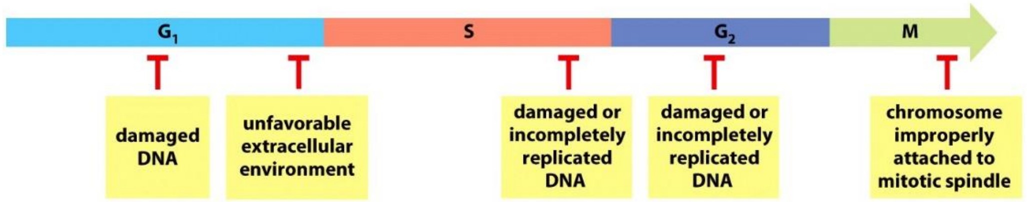
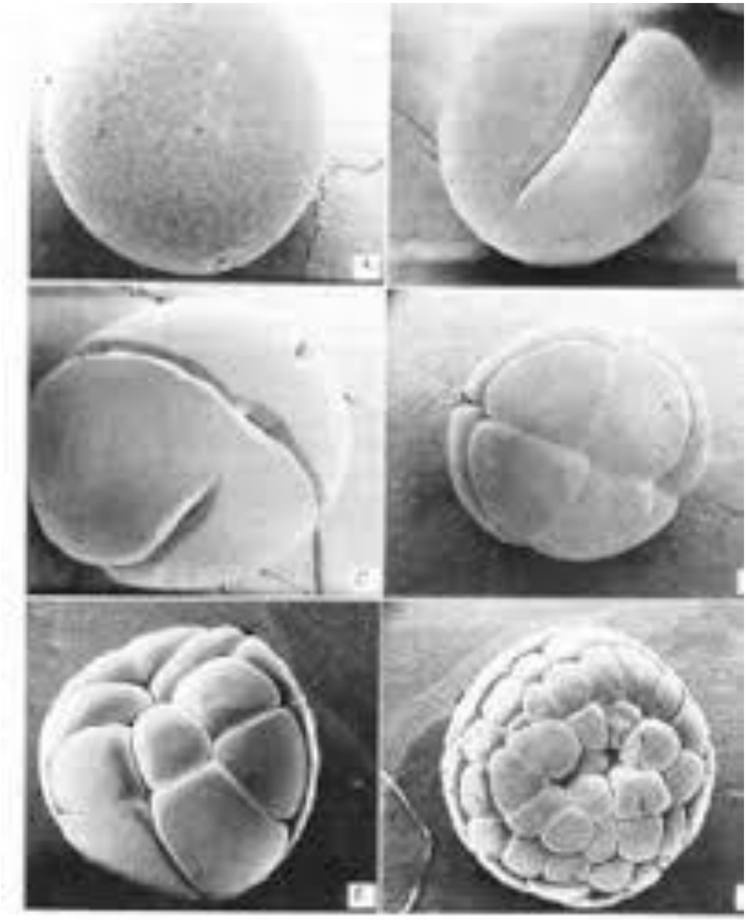

G_1
S
G_2
M
damaged DNA
unfavorable extracellular environment
damaged or incompletely replicated DNA
damaged or incompletely replicated DNA
chromosome improperly attached to mitotic spindle

Figure 18-13 Essential Cell Biology 3/e (© Garland Science 2010)

O processo pode ser interrompido em vários pontos!

Figure 18-3 *Essential Cell Biology* (© Garland Science 2010)

Primeiros estudo do controle de ciclo celular…



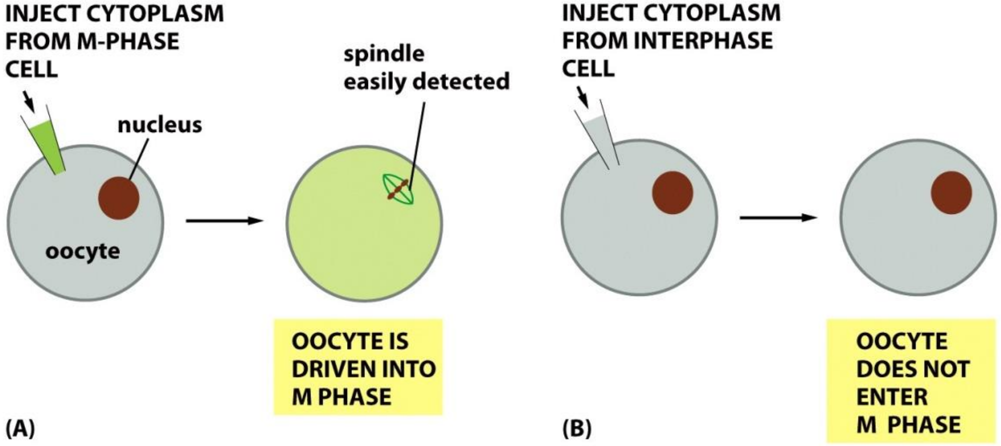
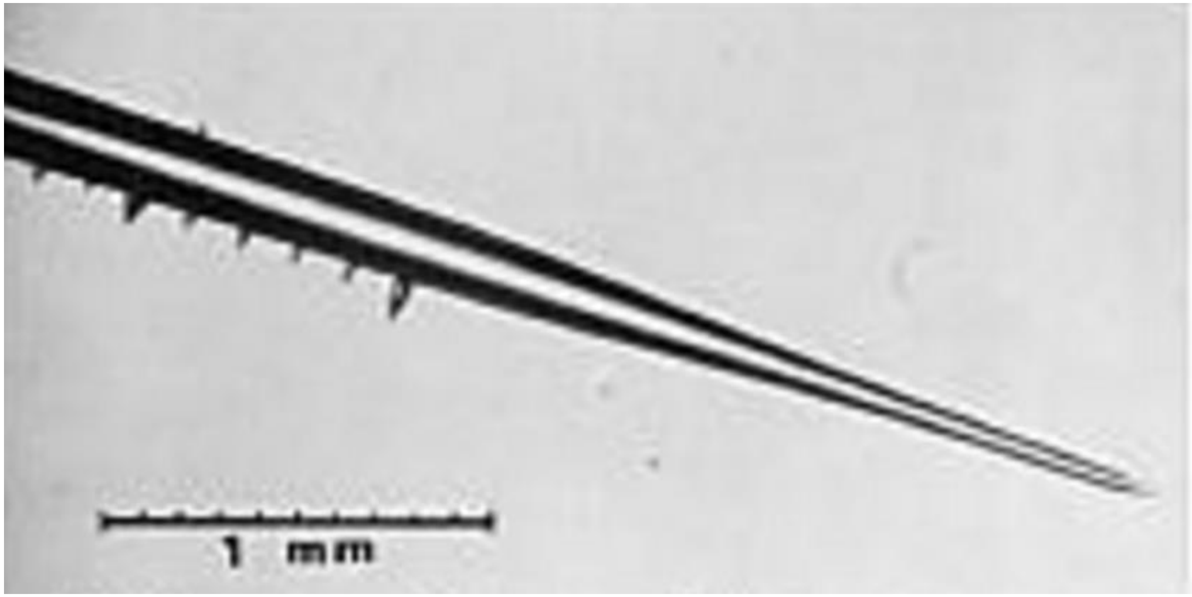

INJECT CYTOPLASM FROM M-PHASE CELL
nucleus
oocyte
spindle easily detected
OOCYTE IS DRIVEN INTO M PHASE
(A)
INJECT CYTOPLASM FROM INTERPHASE CELL
OOCYTE DOES NOT ENTER M PHASE
(B)

Figure 18-7 Essential Cell Biology 3/e (© Garland Science 2010)

Fase S vital – sem crescimento celular antes da divisão!!!

Cytoplasmic Control of Nuclear Behavior during Meiotic Maturation of Frog Oocytes[1]

YOSHIO MASUI[2] AND CLEMENT L. MARKERT
Department of Biology, Yale University, New Haven, Connecticut 065



CADA FASE É VARIÁVEL TEMPORALMENTE

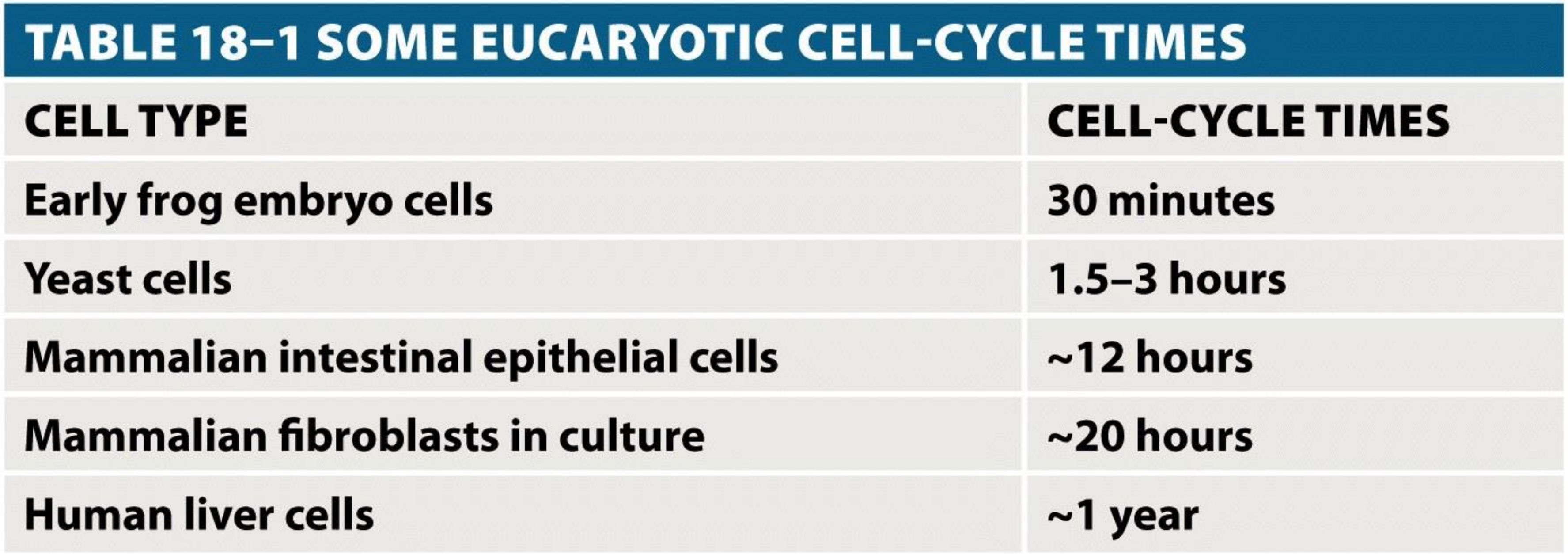


TABLE 18–1 SOME EUCARYOTIC CELL-CYCLE TIMES

CELL TYPE	CELL-CYCLE TIMES
Early frog embryo cells	30 minutes
Yeast cells	1.5–3 hours
Mammalian intestinal epithelial cells	~12 hours
Mammalian fibroblasts in culture	~20 hours
Human liver cells	~1 year

Table 18-1 Essential Cell Biology 3/e (© Garland Science 2010)

DOIS GRUPOS DE PROTEÍNAS CHAVES

✓ **Cinases dependente de Ciclinas (Cdk):** enzimas que fosforilam (adicionam grupamentos fosfatos) à serina e treonina de enzimas chaves.

✓ **Ciclinas:** são proteínas que se ligam às Cdks controlando sua capacidade de fosforilação de proteínas; permitem que elas atuem como enzimas (ativação) e seu direcionamento.

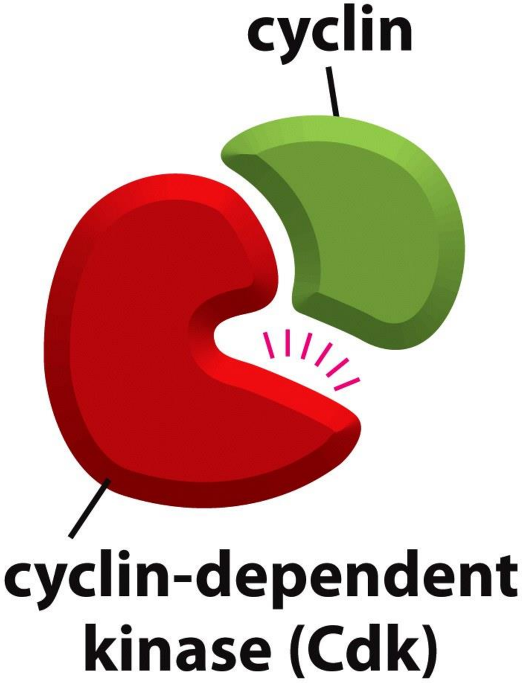
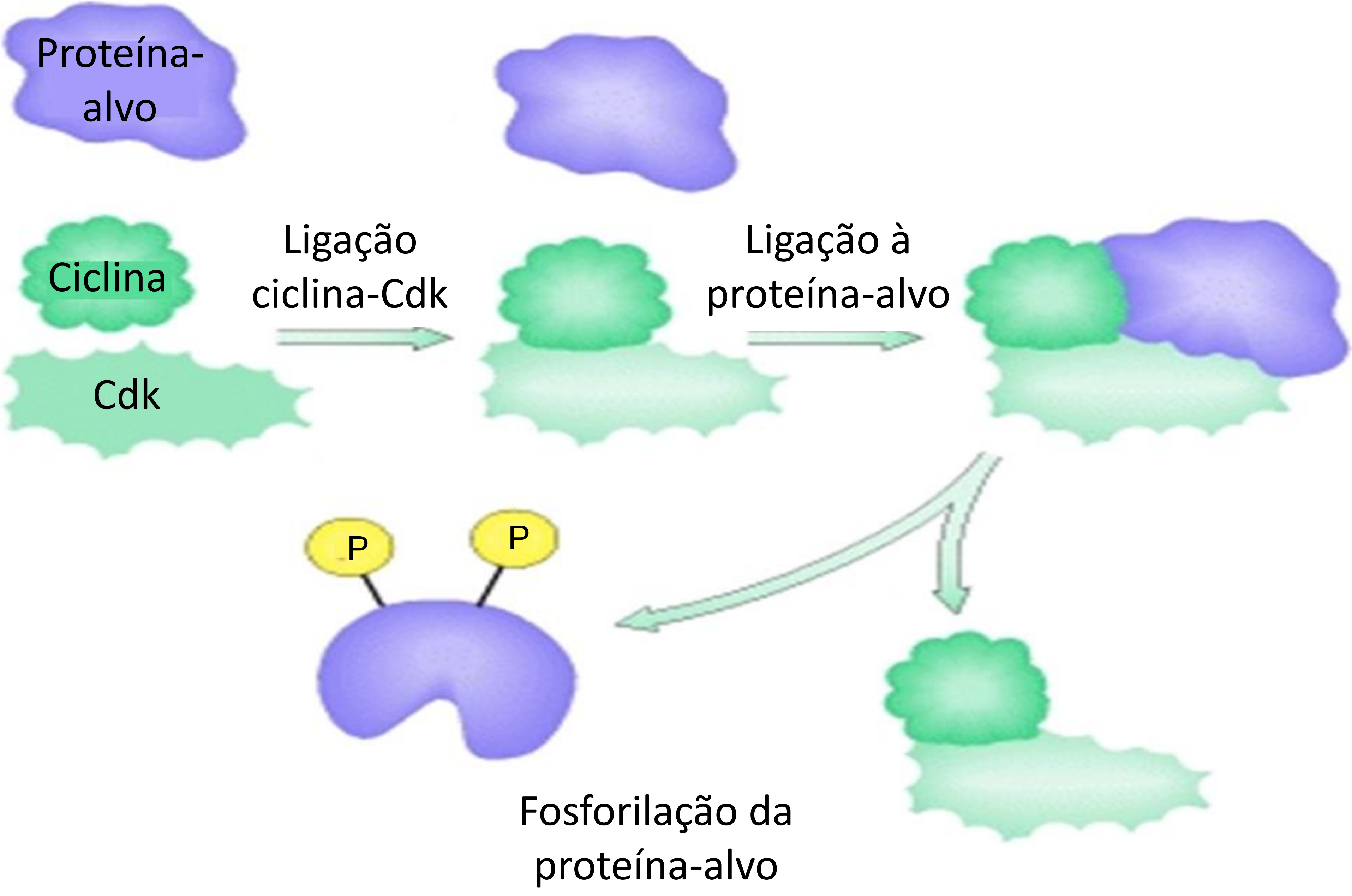


Figure 18-4 Essential Cell Biology 3/e (© Garland Science 2010)

COMPLEXO CICLINA-Cdk



Proteína-alvo

Ciclina

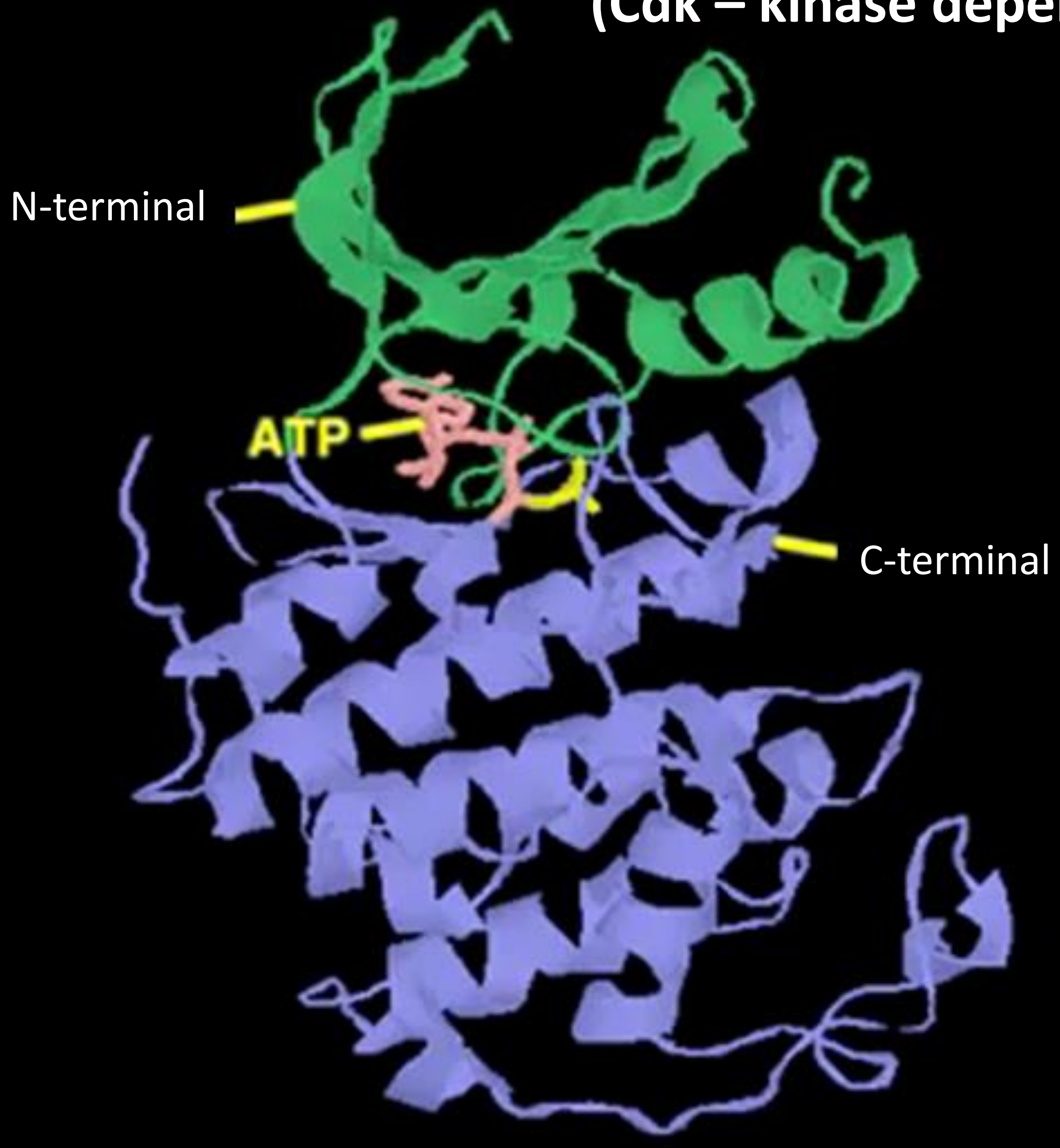
Cdk

Ligação ciclina-Cdk

Ligação à proteína-alvo

Fosforilação da proteína-alvo

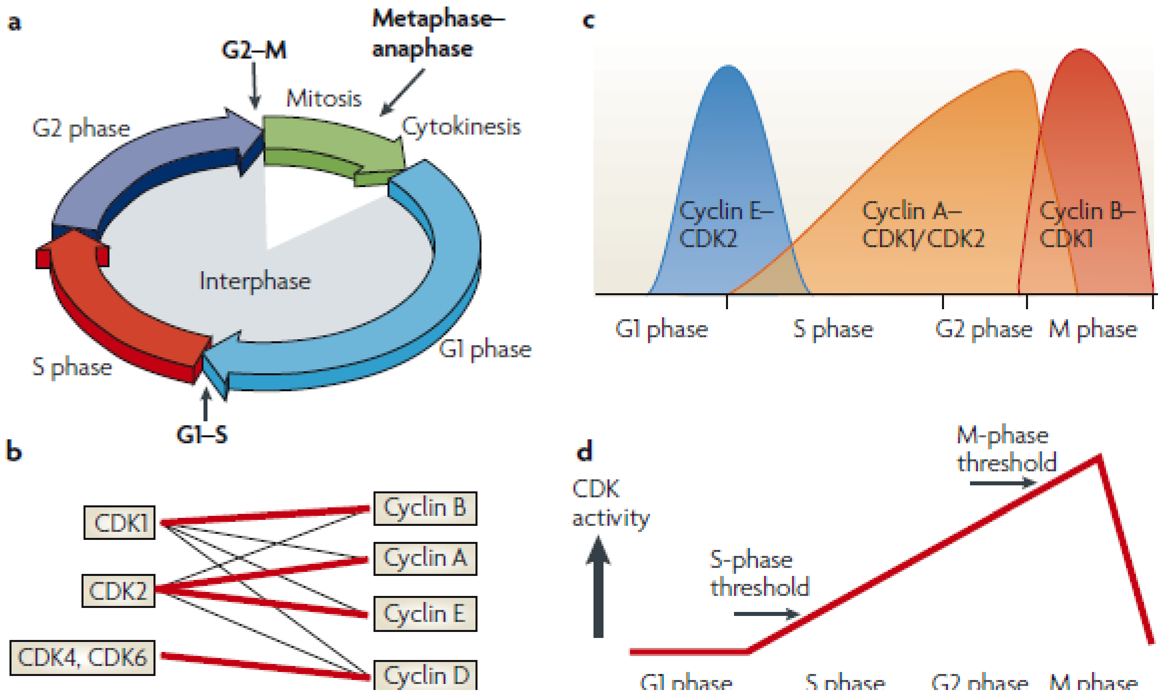
(Cdk – kinase dependente de ciclina)


N-terminal
ATP
C-terminal

OPINION

Cyclin-dependent kinases and cell-cycle transitions: does one fit all?

Helfrid Hochegger, Shunichi Takeda and Tim Hunt


a
G2–M
Metaphase–anaphase
Mitosis
Cytokinesis
G2 phase
Interphase
G1 phase
S phase
G1–S
b
CDK1
CDK2
CDK4, CDK6
Cyclin B
Cyclin A
Cyclin E
Cyclin D
c
Cyclin E–CDK2
Cyclin A–CDK1/CDK2
Cyclin B–CDK1
G1 phase
S phase
G2 phase
M phase
d
CDK activity
S-phase threshold
M-phase threshold
G1 phase
S phase
G2 phase
M phase

A CONCENTRAÇÃO DAS CICLINAS ALTERA, DAS CDKS NÃO!!

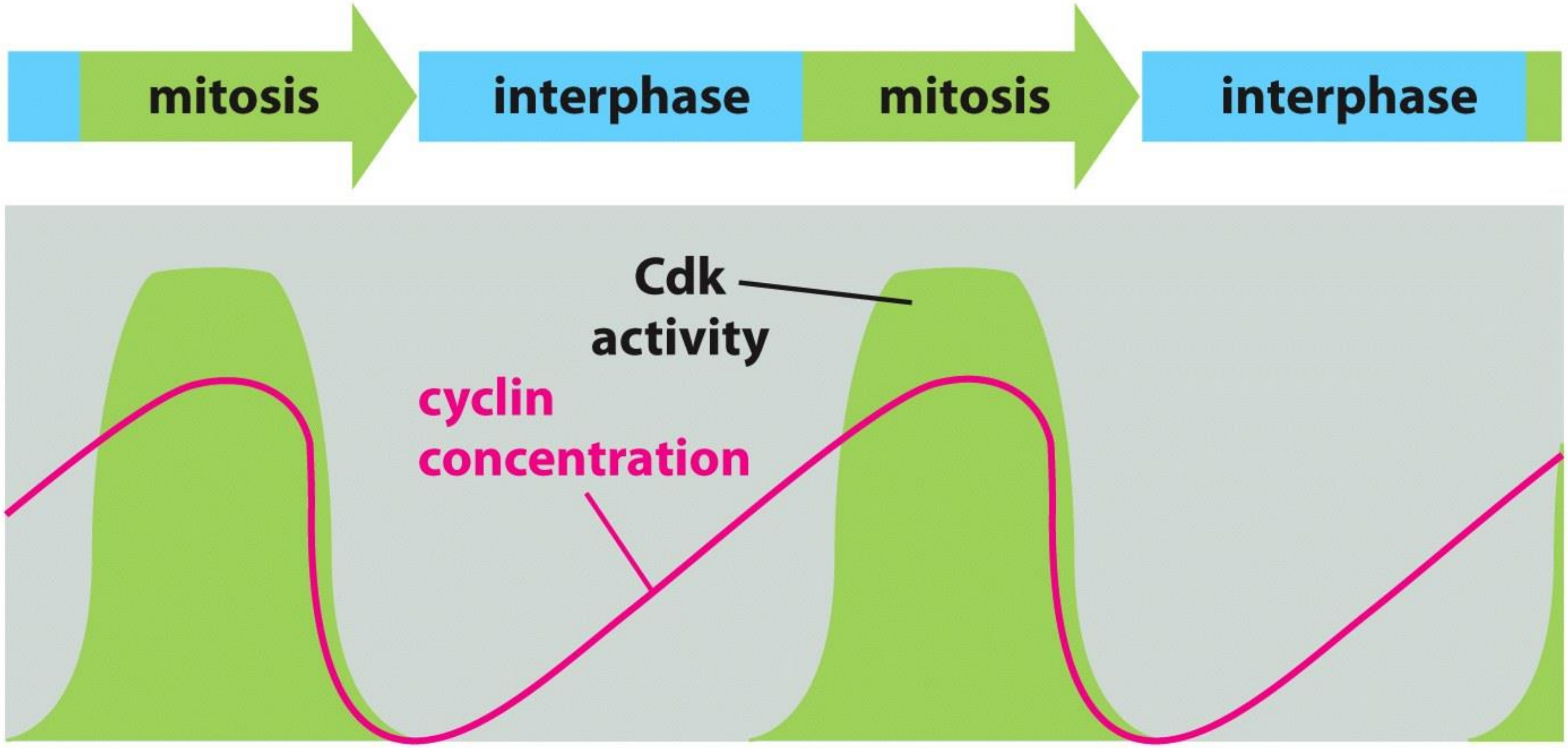
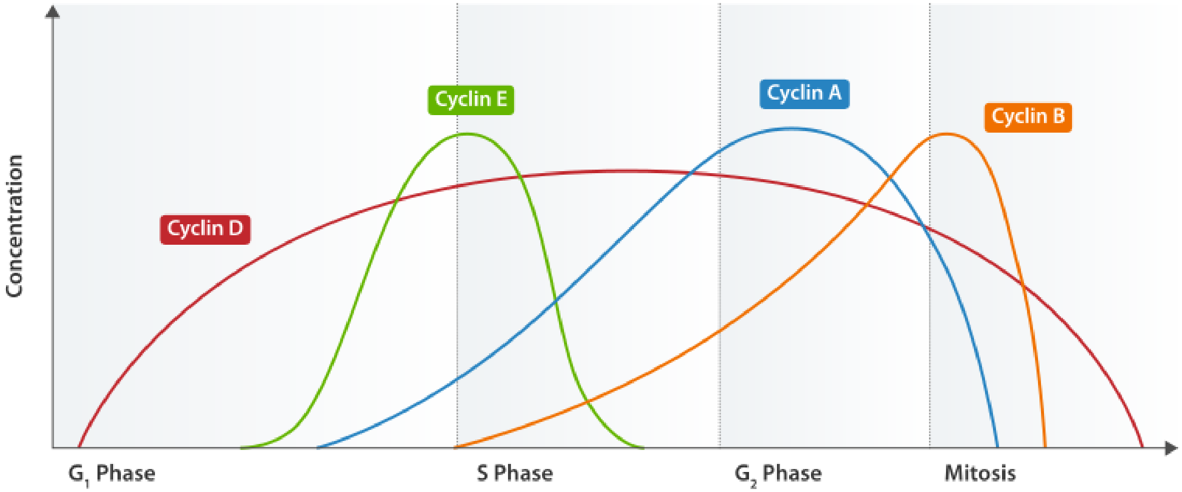


Figure 18-5 Essential Cell Biology 3/e (© Garland Science 2010)

FATORES DE TRANSCRIÇÃO REGULAM A EXPRESSÃO DAS CICLINAS



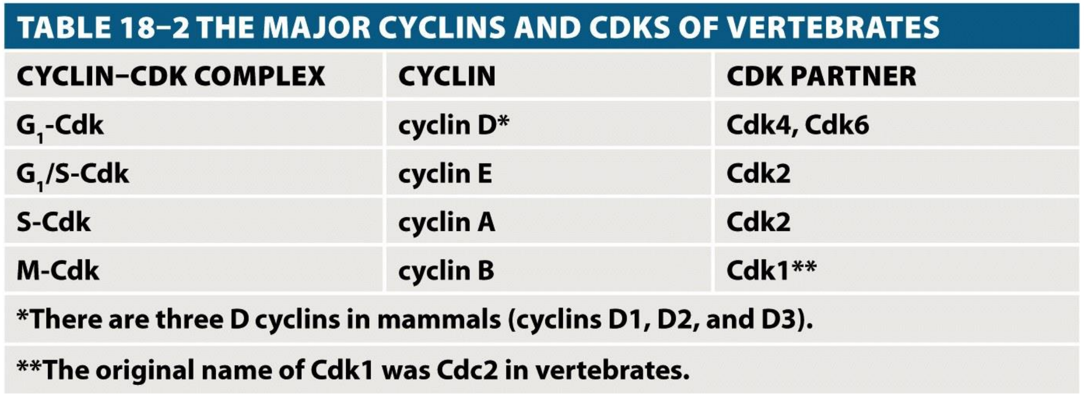


TABLE 18–2 THE MAJOR CYCLINS AND CDKS OF VERTEBRATES

CYCLIN–CDK COMPLEX	CYCLIN	CDK PARTNER
G_1-Cdk	cyclin D*	Cdk4, Cdk6
G_1/S-Cdk	cyclin E	Cdk2
S-Cdk	cyclin A	Cdk2
M-Cdk	cyclin B	Cdk1**

*There are three D cyclins in mammals (cyclins D1, D2, and D3).

**The original name of Cdk1 was Cdc2 in vertebrates.

Table 18-2 Essential Cell Biology 3/e (© Garland Science 2010)

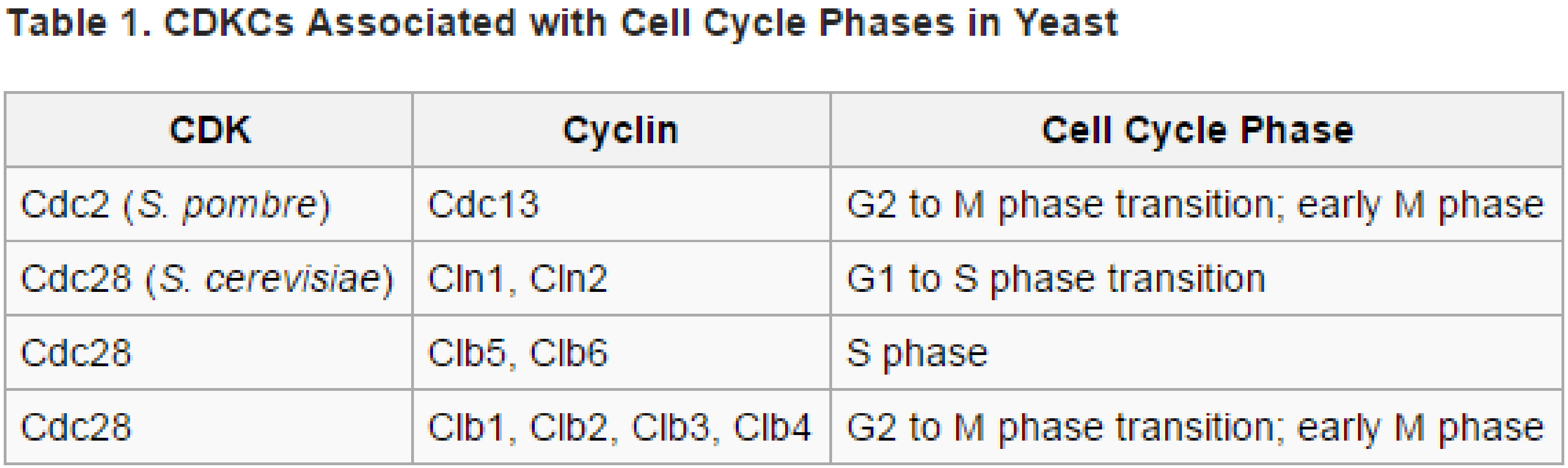


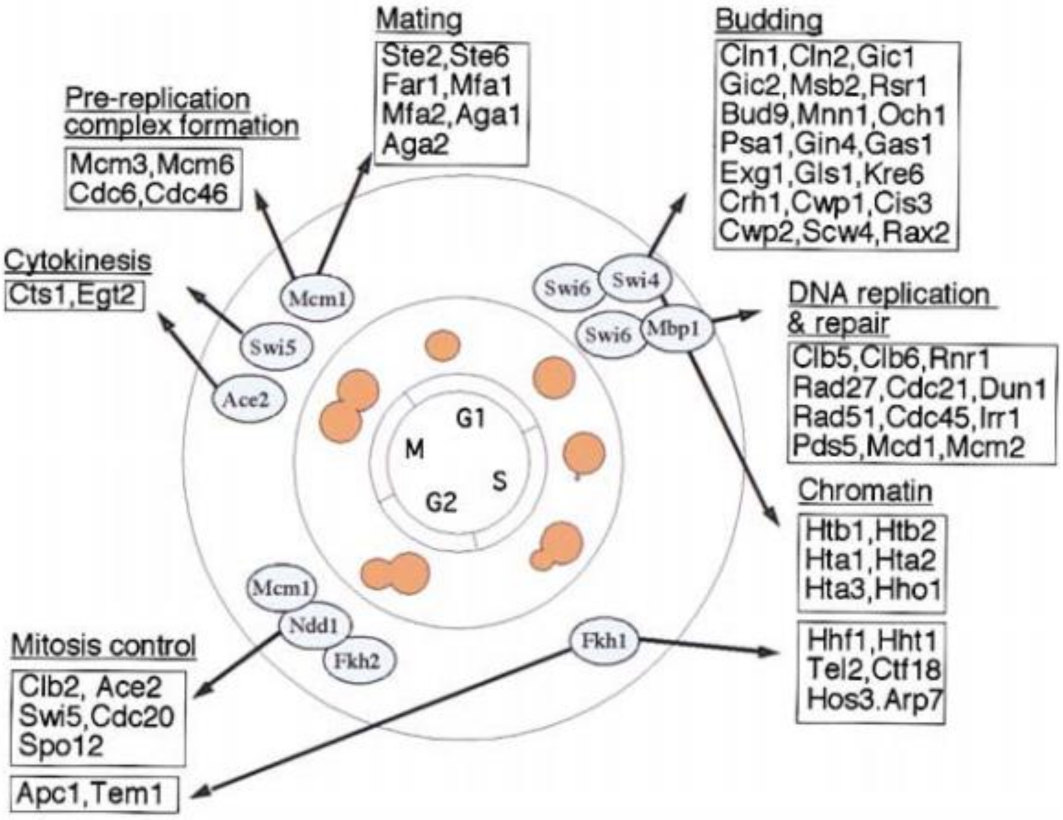
Table 1. CDKCs Associated with Cell Cycle Phases in Yeast

CDK	Cyclin	Cell Cycle Phase
Cdc2 (*S. pombre*)	Cdc13	G2 to M phase transition; early M phase
Cdc28 (*S. cerevisiae*)	Cln1, Cln2	G1 to S phase transition
Cdc28	Clb5, Clb6	S phase
Cdc28	Clb1, Clb2, Clb3, Clb4	G2 to M phase transition; early M phase

Necessidade de estudos para entender a sua associação com fatores de transcrição envolvidos no controle do ciclo celular.

Cell, Vol. 106, 697–708, September 21, 2001, Copyright ©2001 by Cell Press

Serial Regulation of Transcriptional Regulators in the Yeast Cell Cycle



Mating
Ste2,Ste6
Far1,Mfa1
Mfa2,Aga1
Aga2

Budding
Cln1,Cln2,Gic1
Gic2,Msb2,Rsr1
Bud9,Mnn1,Och1
Psa1,Gin4,Gas1
Exg1,Gls1,Kre6
Crh1,Cwp1,Cis3
Cwp2,Scw4,Rax2

Pre-replication complex formation
Mcm3,Mcm6
Cdc6,Cdc46

Cytokinesis
Cts1,Egt2

DNA replication & repair
Clb5,Clb6,Rnr1
Rad27,Cdc21,Dun1
Rad51,Cdc45,Irr1
Pds5,Mcd1,Mcm2

Chromatin
Htb1,Htb2
Hta1,Hta2
Hta3,Hho1

Hhf1,Hht1
Tel2,Ctf18
Hos3,Arp7

Mitosis control
Clb2, Ace2
Swi5,Cdc20
Spo12

Apc1,Tem1

EXISTEM CINASES E FOSFATASES PARA CADA CDK

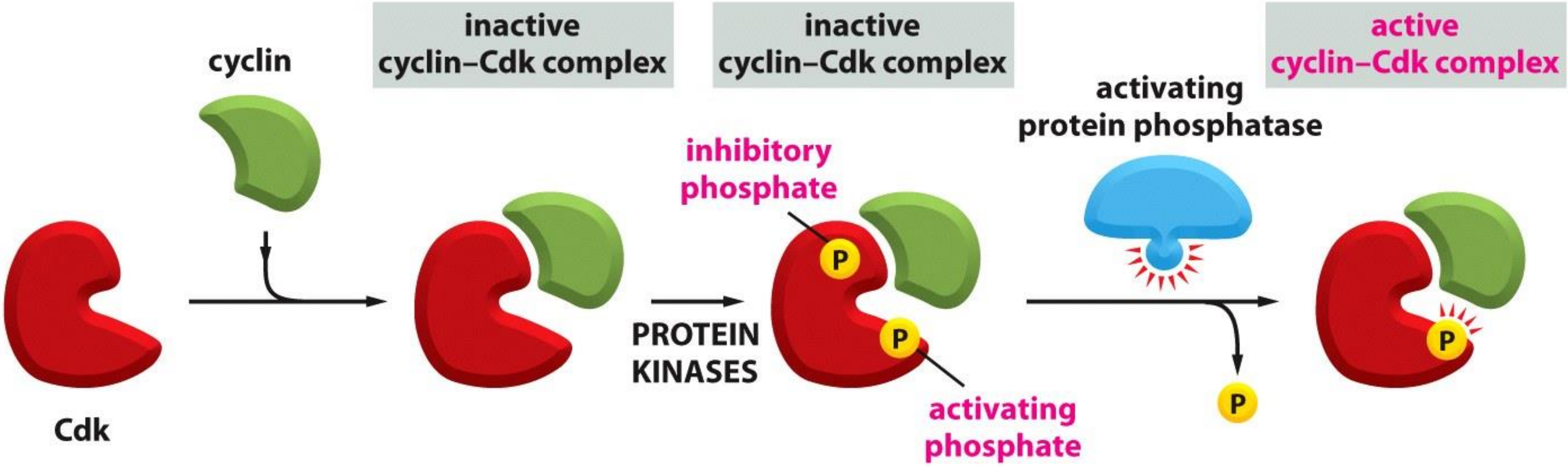

cyclin
inactive cyclin–Cdk complex
inactive cyclin–Cdk complex
active cyclin–Cdk complex
activating protein phosphatase
inhibitory phosphate
P
P
P
P
PROTEIN KINASES
activating phosphate
Cdk

Figure 18-9 Essential Cell Biology 3/e (© Garland Science 2010)

Na verdade a ciclina fosforila a CdK em três sítios, 1 importante para sua ativação e dois que a mantem inativada até a atividade de uma fosfatase

A QUANTIDADE DE CICLINAS ESPECIFICAS É VITAL PARA O CONTROLE DO CICLO CELLULAR…

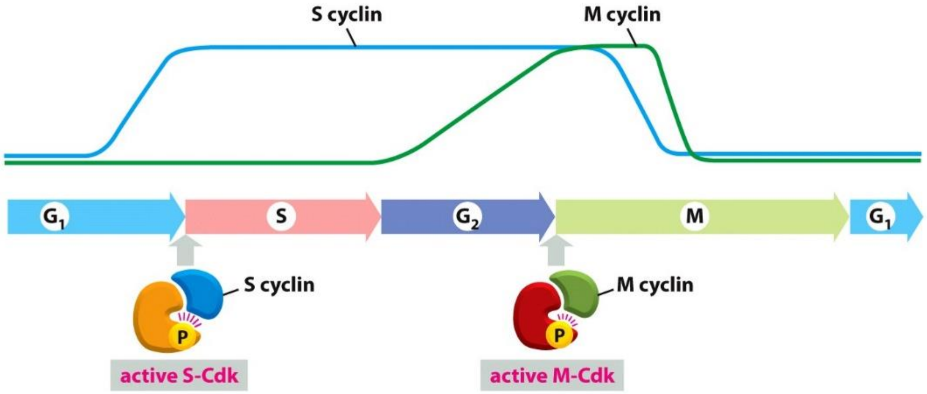

S cyclin
M cyclin
G1
S
G2
M
G1
S cyclin
P
M cyclin
P
active S-Cdk
active M-Cdk

Figure 18-10 Essential Cell Biology 3/e (© Garland Science 2010)

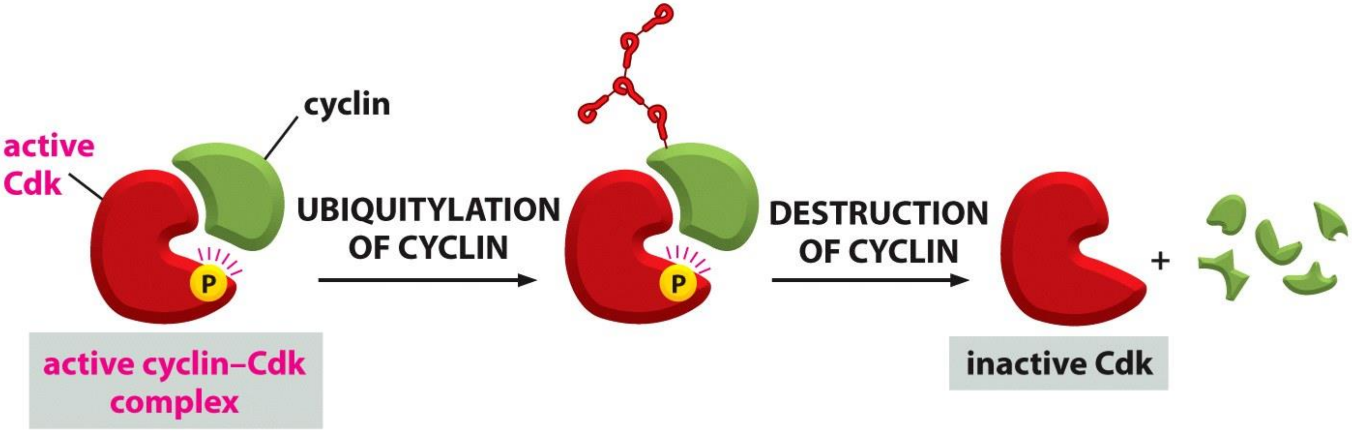

cyclin
active Cdk
P
UBIQUITYLATION OF CYCLIN
P
DESTRUCTION OF CYCLIN
+
active cyclin–Cdk complex
inactive Cdk

Figure 18-11 Essential Cell Biology 3/e (© Garland Science 2010)

Um dos mecanismos de controle é a ubiquitinação e dragração de ciclinas

RATCHETS AND CLOCKS: THE CELL CYCLE, UBIQUITYLATION AND PROTEIN TURNOVER

Steven I. Reed

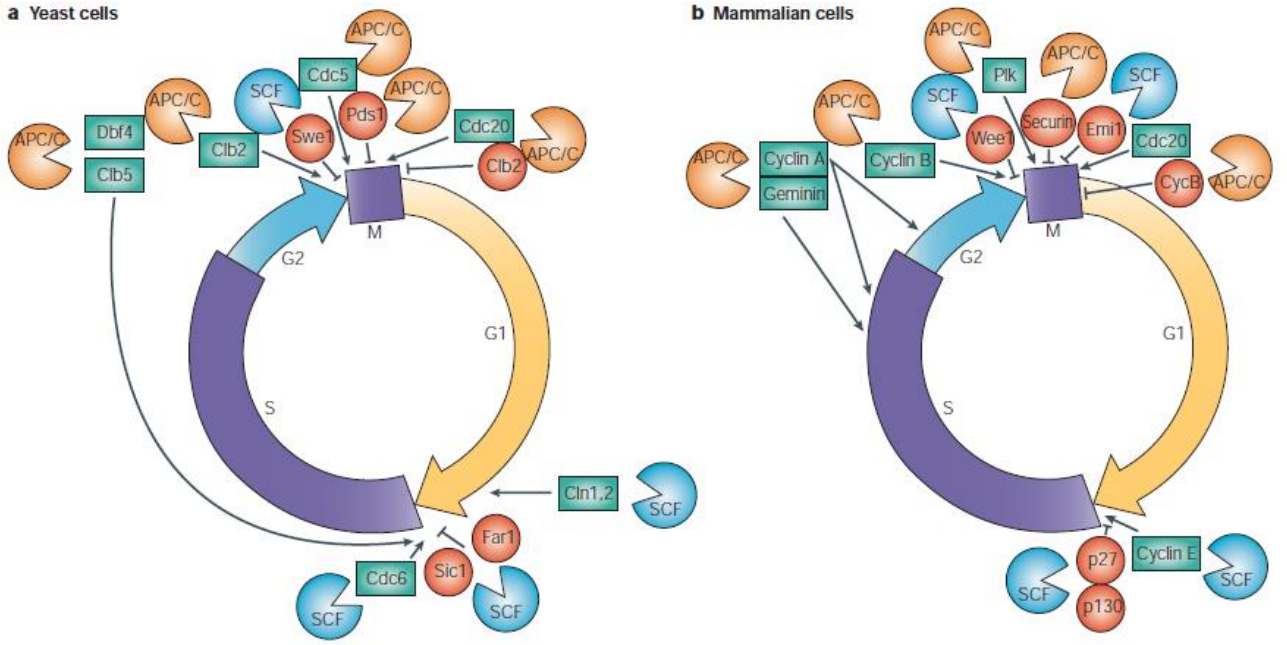

a Yeast cells
APC/C
Dbf4
Clb5
APC/C
Clb2
SCF
Swe1
Cdc5
Pds1
APC/C
APC/C
Cdc20
Clb2
APC/C
M
G2
G1
S
Cln1,2
SCF
Far1
Cdc6
Sic1
SCF
SCF
b Mammalian cells
APC/C
Cyclin A
Geminin
APC/C
Cyclin B
SCF
Wee1
APC/C
Plk
Securin
APC/C
Emi1
SCF
Cdc20
CycB
APC/C
M
G2
G1
S
p27
p130
SCF
Cyclin E
SCF

Figure 1 | **Key cell-cycle regulatory proteins targeted by ubiquitin-mediated proteolysis.** The G1, S, G2 and M phases of the cell cycle are depicted. **a** | shows yeast cells, and **b** | shows mammalian cells. The class of protein-ubiquitin ligase that is responsible for ubiquitylation of the respective proteins is indicated. See TABLE 1 for a more extensive list and more details. Positive cell-cycle regulators are shown as green rectangles, whereas negative regulators are depicted as red circles. Note that cyclin-B–Clb2 is both a positive and negative cell-cycle regulator. APC/C, anaphase-promoting complex/cyclosome; G1 and G2, Gap phases 1 and 2; M, Mitosis; S, DNA synthesis; SCF, Skp1/Cullin/F-box protein.

EXEMPLOS DE ATIVIDADE DE CDKs

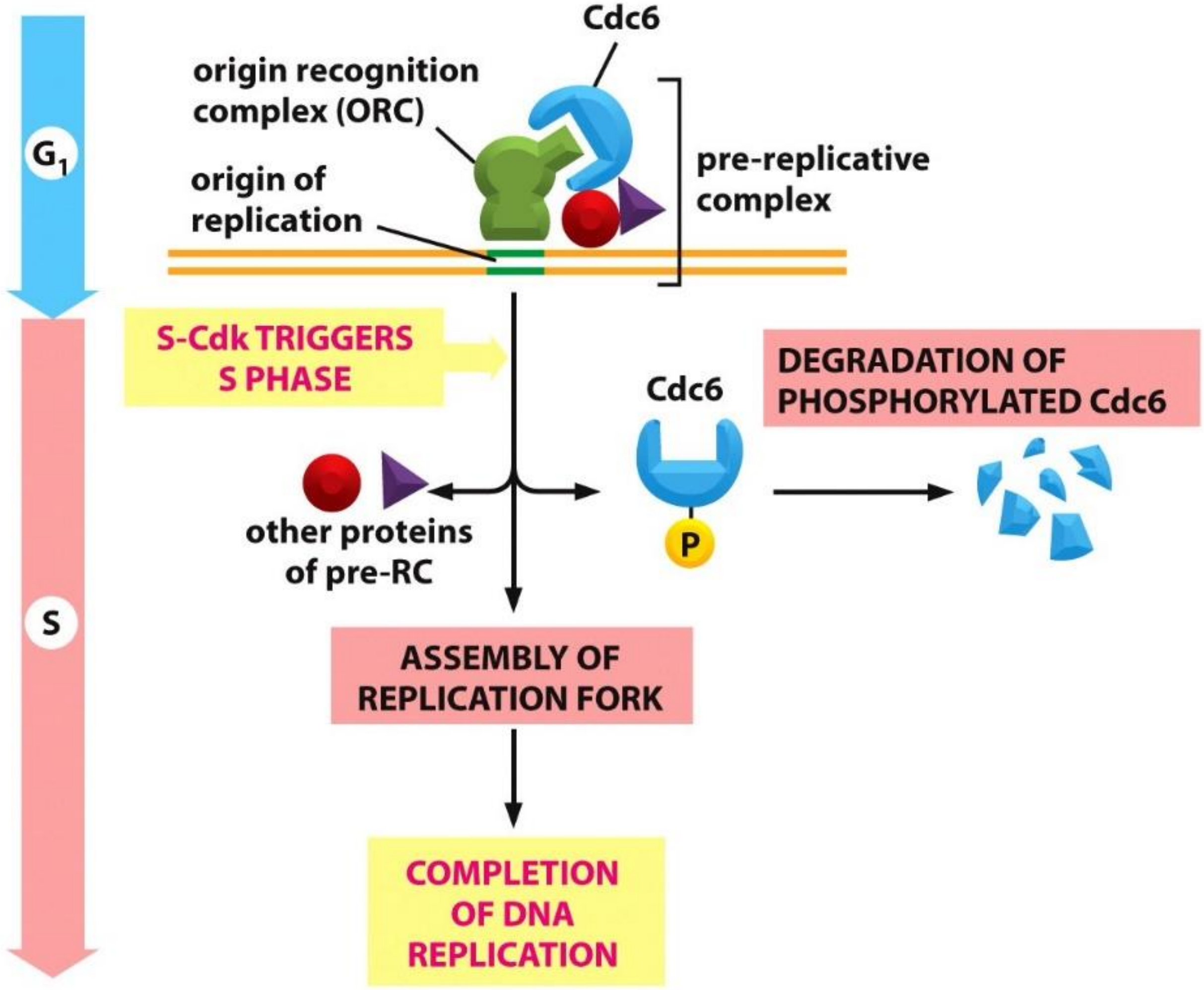

Cdc6
origin recognition complex (ORC)
origin of replication
pre-replicative complex
G1
S-Cdk TRIGGERS S PHASE
Cdc6
DEGRADATION OF PHOSPHORYLATED Cdc6
other proteins of pre-RC
P
S
ASSEMBLY OF REPLICATION FORK
COMPLETION OF DNA REPLICATION

Figure 18-14 Essential Cell Biology 3/e (© Garland Science 2010)

EXEMPLOS DE ATIVIDADE DE CDKs

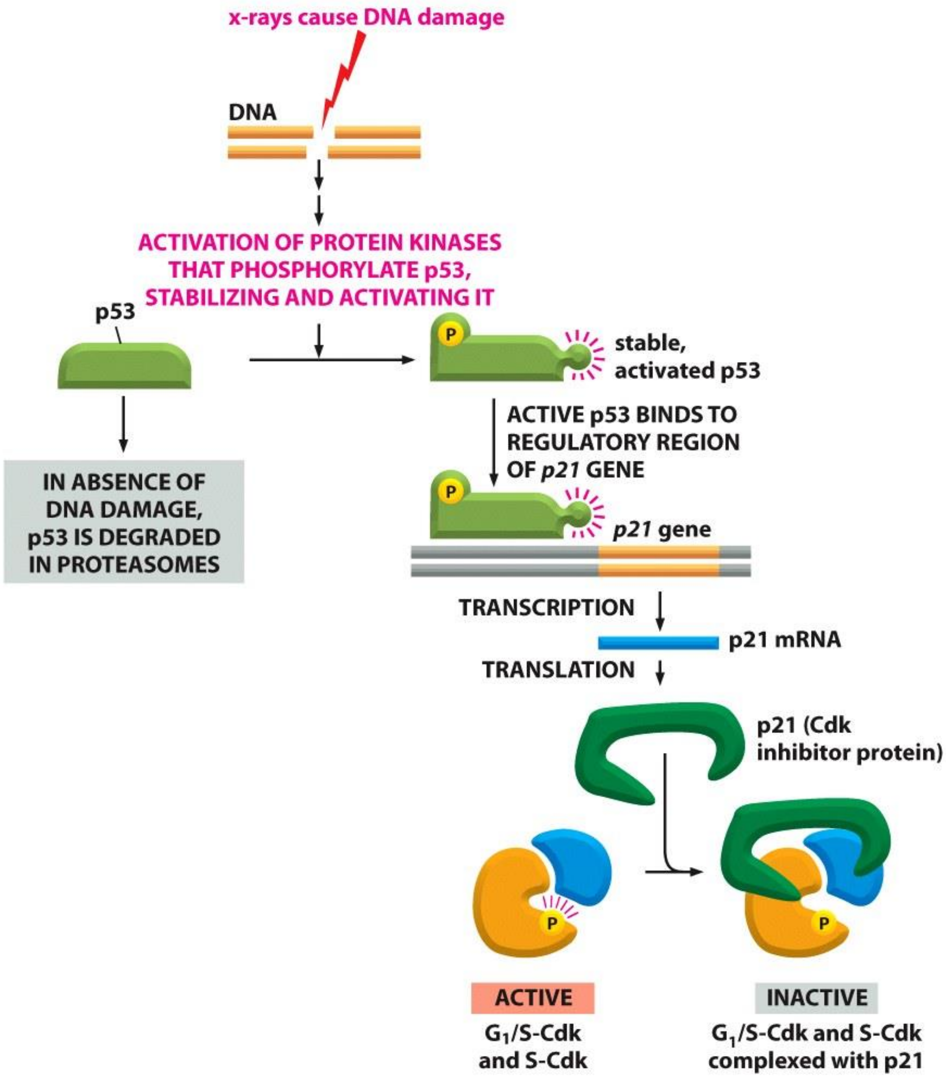

x-rays cause DNA damage
DNA
ACTIVATION OF PROTEIN KINASES THAT PHOSPHORYLATE p53, STABILIZING AND ACTIVATING IT
p53
P
stable, activated p53
IN ABSENCE OF DNA DAMAGE, p53 IS DEGRADED IN PROTEASOMES
ACTIVE p53 BINDS TO REGULATORY REGION OF *p21* GENE
P
p21 gene
TRANSCRIPTION
p21 mRNA
TRANSLATION
p21 (Cdk inhibitor protein)
P
P
ACTIVE
G_1/S-Cdk and S-Cdk
INACTIVE
G_1/S-Cdk and S-Cdk complexed with p21

Figure 18-16 Essential Cell Biology 3/e (© Garland Science 2010)

Cell Death and Differentiation (2018) 25, 114–132
Official journal of the Cell Death Differentiation Association

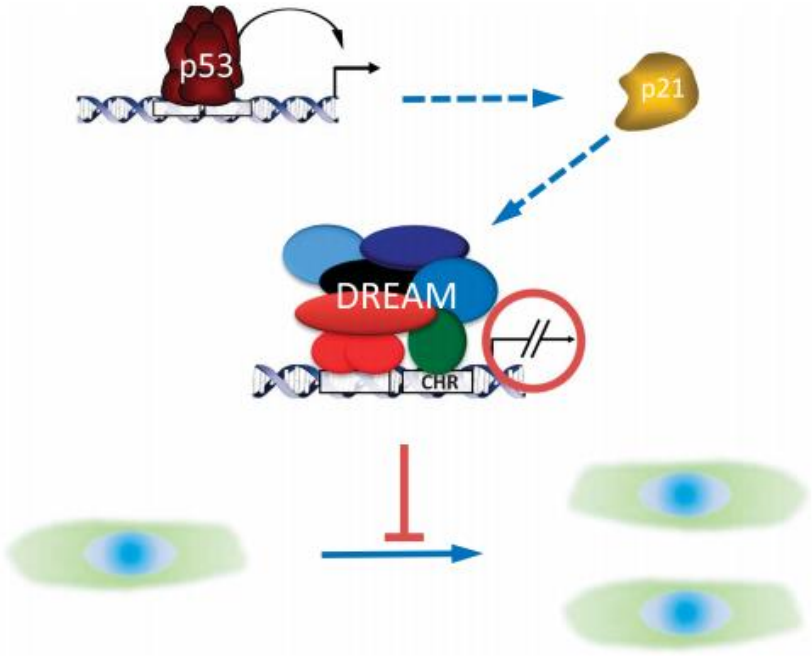
www.nature.com/cdd

OPEN

Review

Cell cycle arrest through indirect transcriptional repression by p53: I have a DREAM

Kurt Engeland[1]



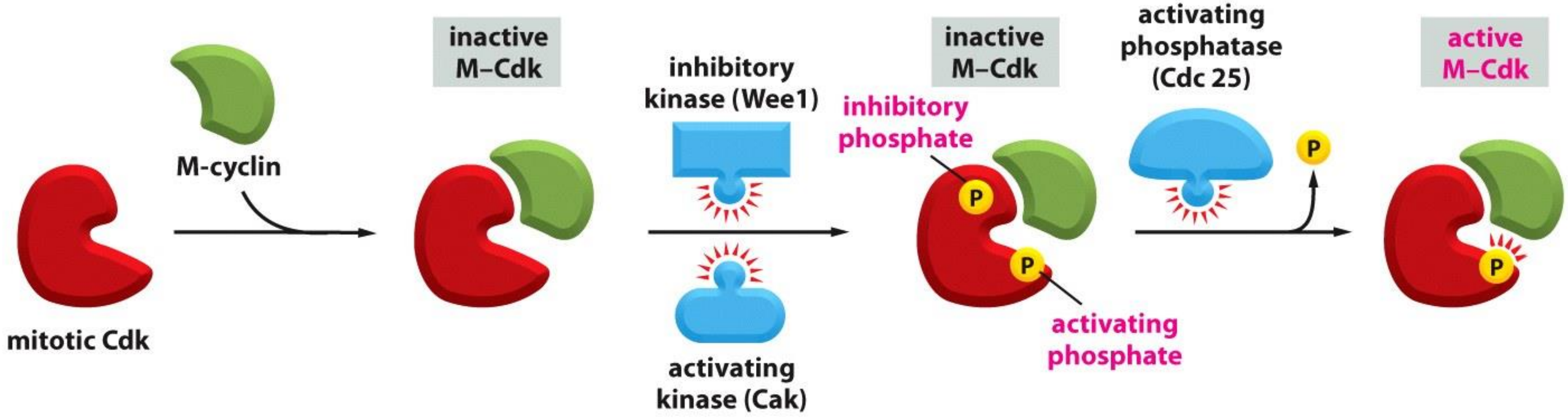

mitotic Cdk
M-cyclin
inactive M–Cdk
inhibitory kinase (Wee1)
activating kinase (Cak)
inactive M–Cdk
inhibitory phosphate
activating phosphate
P
activating phosphatase (Cdc 25)
active M–Cdk

Figure 18-17 Essential Cell Biology 3/e (© Garland Science 2010)

No caso da Cdc25 há um processo de retroalimentação positiva de sua atividade

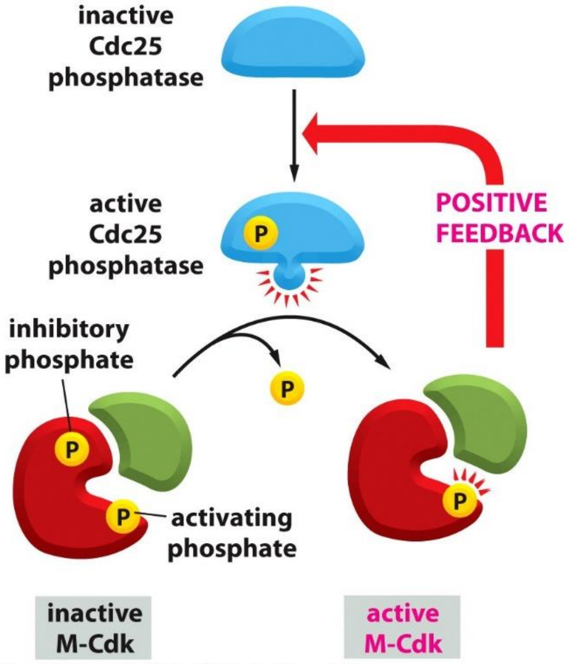

inactive Cdc25 phosphatase
active Cdc25 phosphatase
POSITIVE FEEDBACK
inhibitory phosphate
activating phosphate
P
inactive M-Cdk
active M-Cdk

Figure 18-18 Essential Cell Biology 3/e (© Garland Science 2010)

G1-Cdk: decisão da célula entrar ou não em divisão e é ativado por fatores extracelulares – **VITAL NO CONTROLE DE TUMORES**

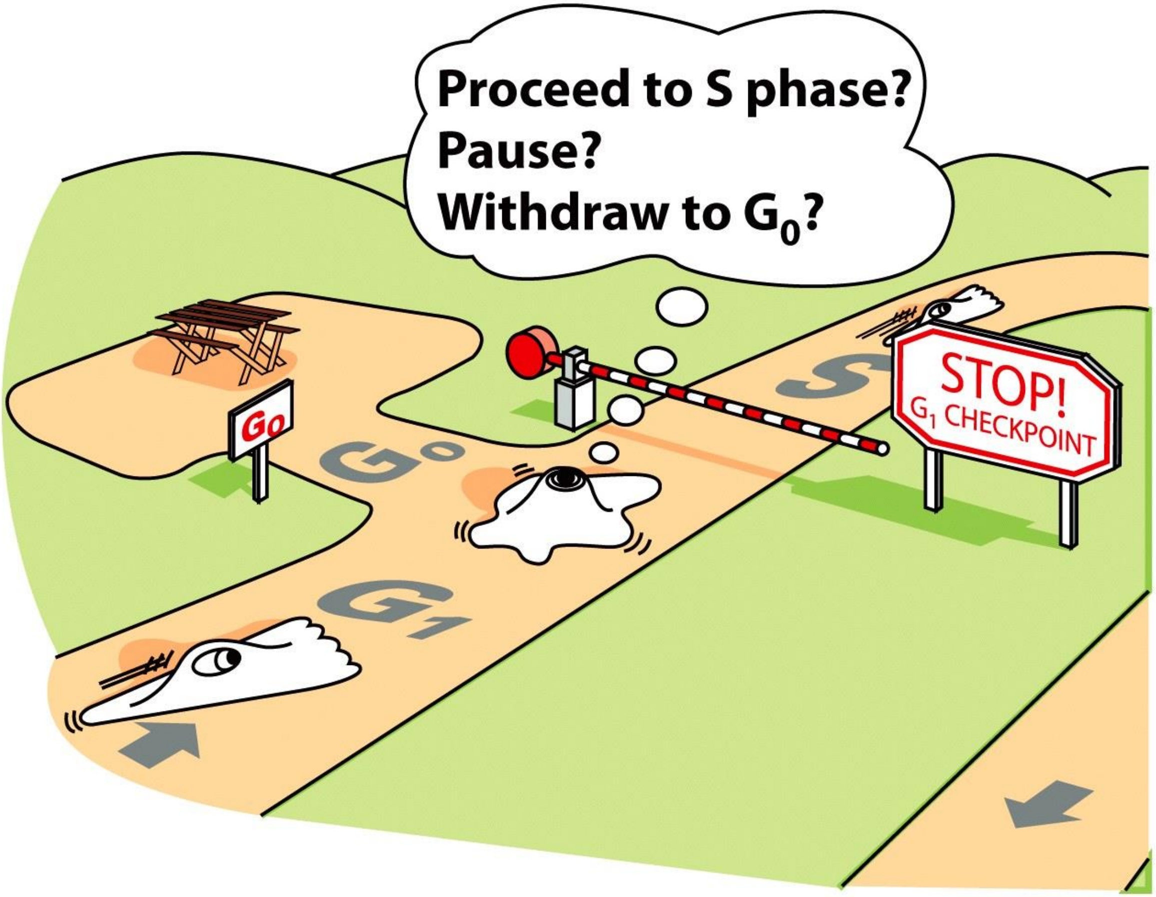
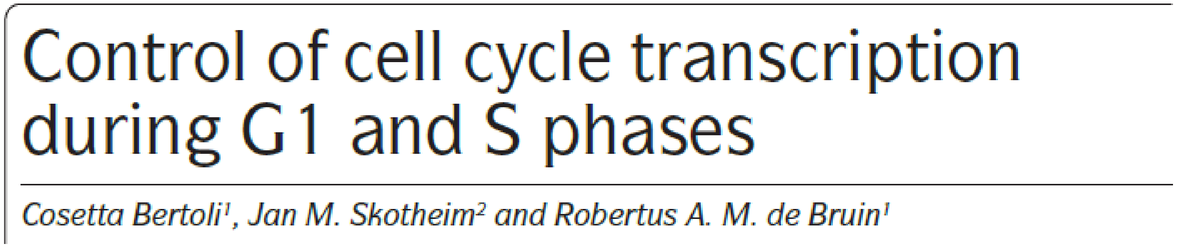

Proceed to S phase?
Pause?
Withdraw to G_0?
Go
G_0
G_1
S
STOP!
G_1 CHECKPOINT

Figure 18-12 Essential Cell Biology 3/e (© Garland Science 2010)



Control of cell cycle transcription during G1 and S phases

Cosetta Bertoli[1], Jan M. Skotheim[2] and Robertus A. M. de Bruin[1]

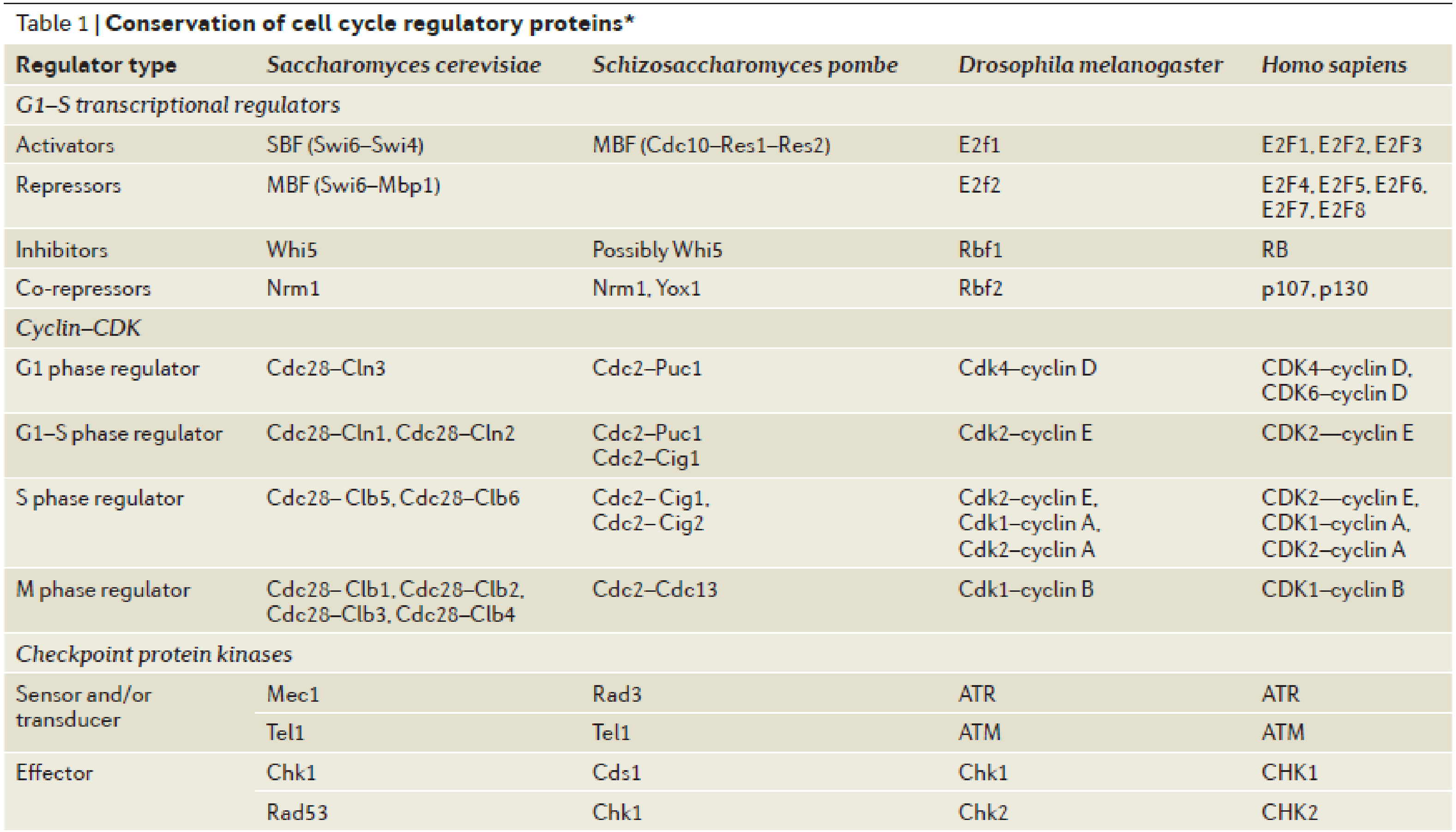
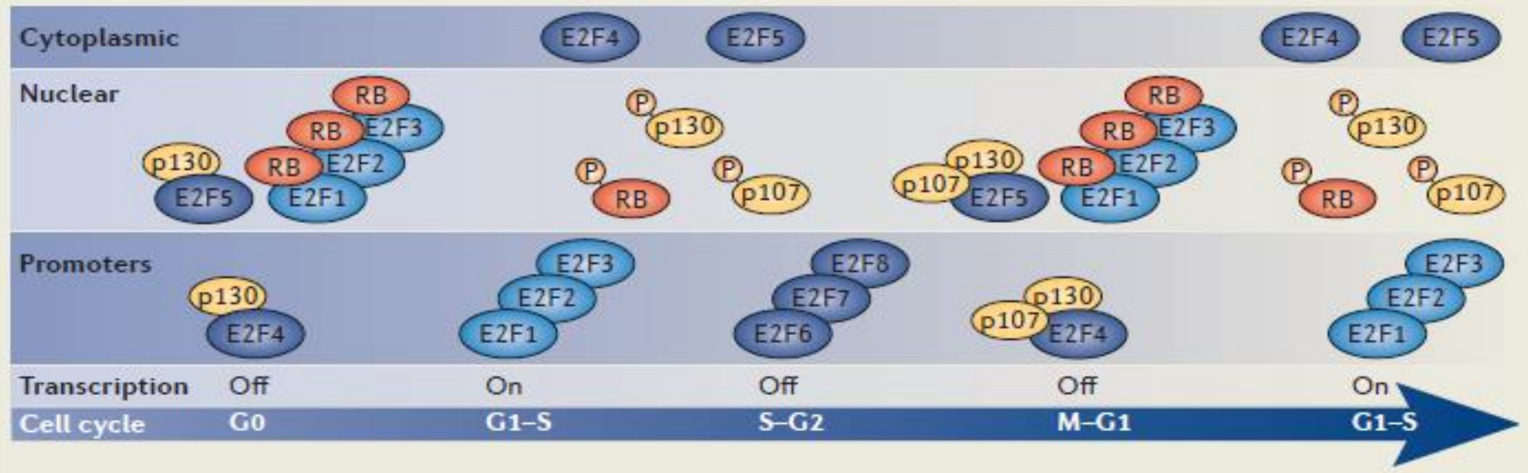


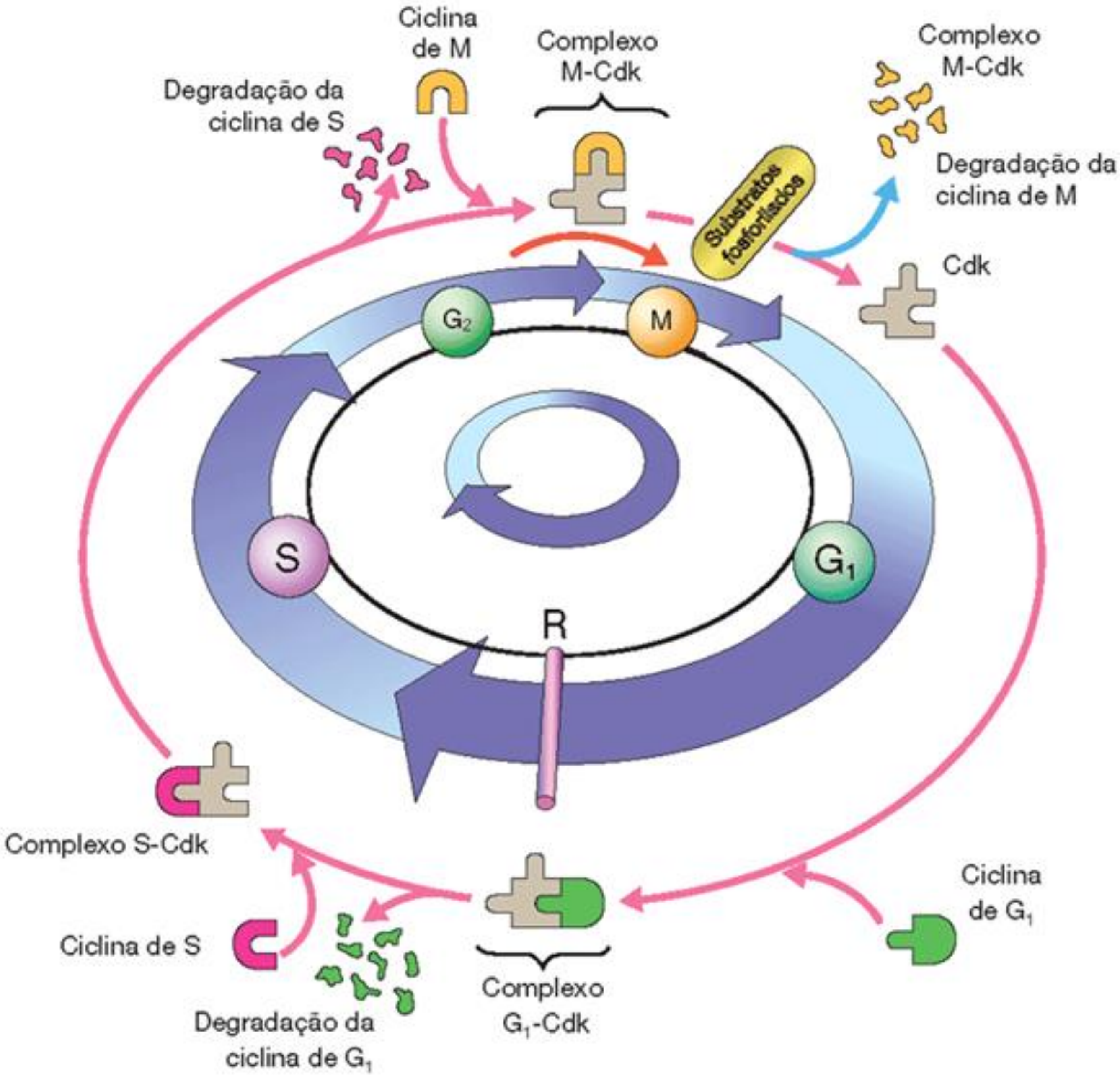
Table 1 | **Conservation of cell cycle regulatory proteins***

Regulator type	***Saccharomyces cerevisiae***	***Schizosaccharomyces pombe***	***Drosophila melanogaster***	***Homo sapiens***
G1–S transcriptional regulators				
Activators	SBF (Swi6–Swi4)	MBF (Cdc10–Res1–Res2)	E2f1	E2F1, E2F2, E2F3
Repressors	MBF (Swi6–Mbp1)		E2f2	E2F4, E2F5, E2F6, E2F7, E2F8
Inhibitors	Whi5	Possibly Whi5	Rbf1	RB
Co-repressors	Nrm1	Nrm1, Yox1	Rbf2	p107, p130
Cyclin–CDK				
G1 phase regulator	Cdc28–Cln3	Cdc2–Puc1	Cdk4–cyclin D	CDK4–cyclin D, CDK6–cyclin D
G1–S phase regulator	Cdc28–Cln1, Cdc28–Cln2	Cdc2–Puc1 Cdc2–Cig1	Cdk2–cyclin E	CDK2—cyclin E
S phase regulator	Cdc28– Clb5, Cdc28–Clb6	Cdc2– Cig1, Cdc2– Cig2	Cdk2–cyclin E, Cdk1–cyclin A, Cdk2–cyclin A	CDK2—cyclin E, CDK1–cyclin A, CDK2–cyclin A
M phase regulator	Cdc28– Clb1, Cdc28–Clb2, Cdc28–Clb3, Cdc28–Clb4	Cdc2–Cdc13	Cdk1–cyclin B	CDK1–cyclin B
Checkpoint protein kinases				
Sensor and/or transducer	Mec1	Rad3	ATR	ATR
	Tel1	Tel1	ATM	ATM
Effector	Chk1	Cds1	Chk1	CHK1
	Rad53	Chk1	Chk2	CHK2

A família E2F de fatores de transcrição e seu dimeros agem como reguladores transcricionais da fase G1/S.

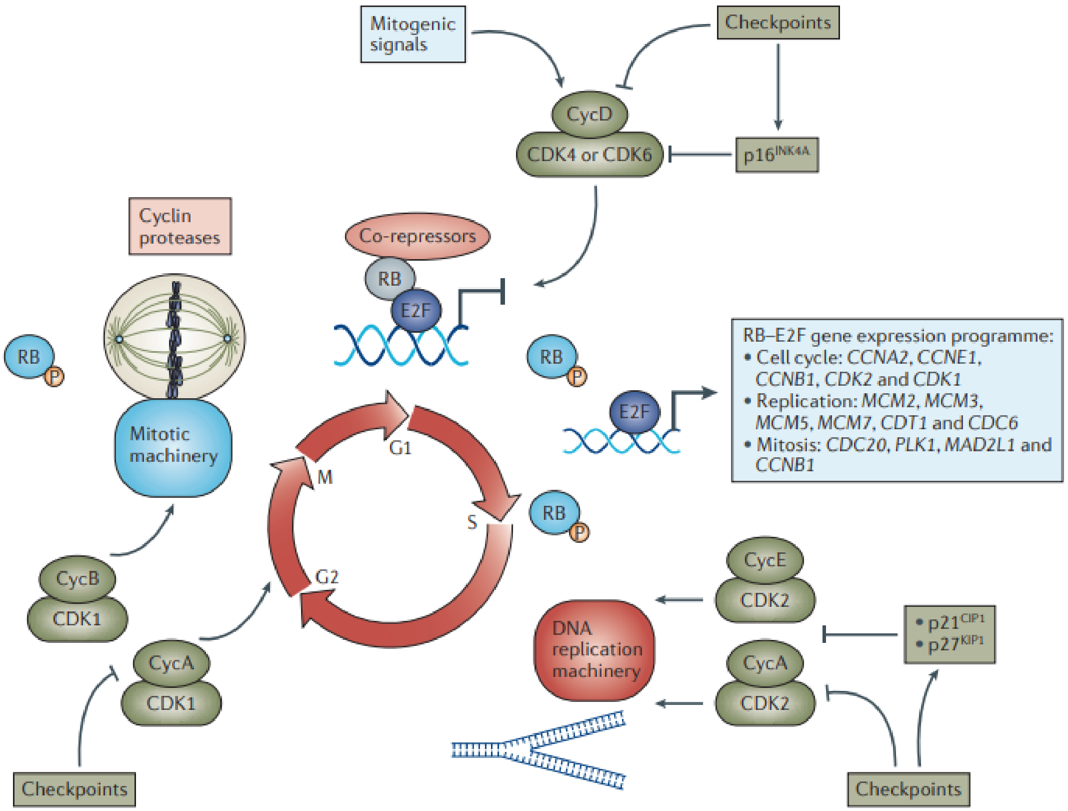

Cytoplasmic
E2F4
E2F5
E2F4
E2F5
Nuclear
RB
RB
E2F3
p130
RB
E2F2
E2F5
E2F1
P
p130
P
RB
P
p107
p130
p107
RB
E2F5
RB
E2F3
RB
E2F2
E2F1
P
p130
P
RB
P
p107
Promoters
p130
E2F4
E2F3
E2F2
E2F1
E2F8
E2F7
E2F6
p130
p107
E2F4
E2F3
E2F2
E2F1
Transcription
Off
On
Off
Off
On
Cell cycle
G0
G1–S
S–G2
M–G1
G1–S

Dimerization partner proteins are omitted for simplicity. Hyperphosphorylation is indicated by 'P'. Promoter binding for individual E2F family members is only indicated when binding has been established during the cell cycle.

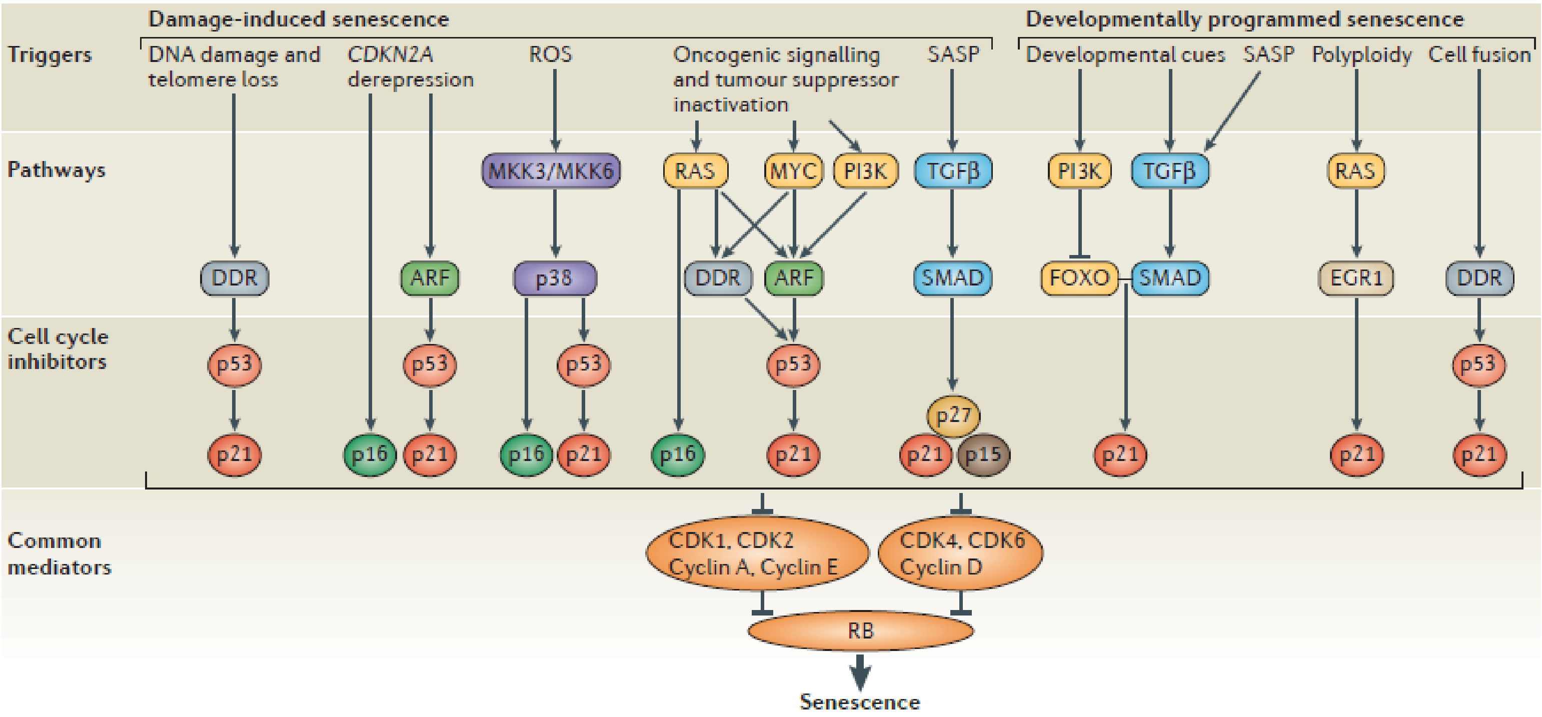

Ciclina de M
Complexo M-Cdk
Complexo M-Cdk
Degradação da ciclina de S
Degradação da ciclina de M
Substratos fosforilados
Cdk
G_2
M
S
G_1
R
Complexo S-Cdk
Ciclina de S
Degradação da ciclina de G_1
Complexo G_1-Cdk
Ciclina de G_1

The history and future of targeting cyclin-dependent kinases in cancer therapy

Uzma Asghar[1], Agnieszka K. Witkiewicz[2], Nicholas C. Turner[3] and Erik S. Knudsen[2]

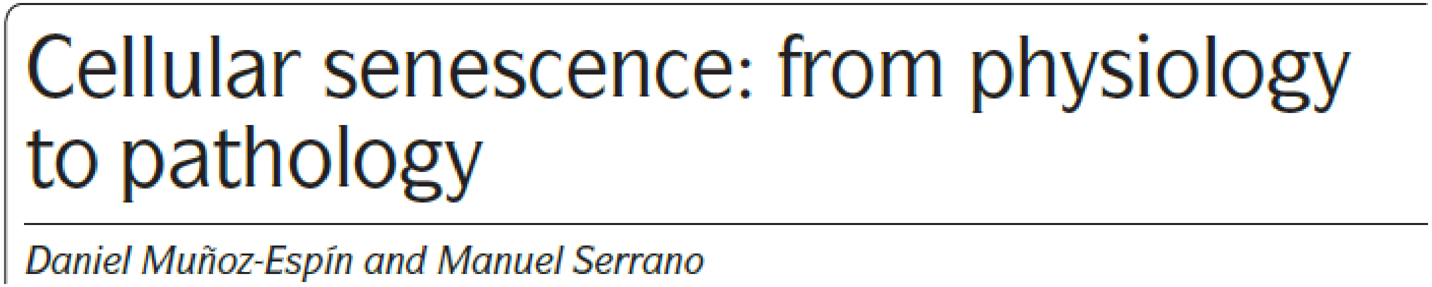

Mitogenic signals
Checkpoints
CycD
CDK4 or CDK6
$p16^{INK4A}$
Cyclin proteases
Co-repressors
RB
E2F
RB
P
Mitotic machinery
RB
P
E2F
G1
M
S
G2
RB
P
CycB
CDK1
CycA
CDK1
CycE
CDK2
DNA replication machinery
CycA
CDK2
• $p21^{CIP1}$
• $p27^{KIP1}$
Checkpoints
Checkpoints

RB–E2F gene expression programme:
- Cell cycle: *CCNA2*, *CCNE1*, *CCNB1*, *CDK2* and *CDK1*
- Replication: *MCM2*, *MCM3*, *MCM5*, *MCM7*, *CDT1* and *CDC6*
- Mitosis: *CDC20*, *PLK1*, *MAD2L1* and *CCNB1*


Damage-induced senescence
Developmentally programmed senescence
Triggers
DNA damage and telomere loss
CDKN2A derepression
ROS
Oncogenic signalling and tumour suppressor inactivation
SASP
Developmental cues
SASP
Polyploidy
Cell fusion
Pathways
MKK3/MKK6
RAS
MYC
PI3K
TGFβ
PI3K
TGFβ
RAS
DDR
ARF
p38
DDR
ARF
SMAD
FOXO
SMAD
EGR1
DDR
Cell cycle inhibitors
p53
p53
p53
p53
p27
p53
p21
p16
p21
p16
p21
p16
p21
p21
p15
p21
p21
p21
Common mediators
CDK1, CDK2 Cyclin A, Cyclin E
CDK4, CDK6 Cyclin D
RB
Senescence

p53 – Regulador transcricional

p21 – inibidor de CDK



Cellular senescence: from physiology to pathology

Daniel Muñoz-Espín and Manuel Serrano

Non-canonical functions of cell cycle cyclins and cyclin-dependent kinases

Per Hydbring[1,2], Marcos Malumbres[3] and Piotr Sicinski[1,2]

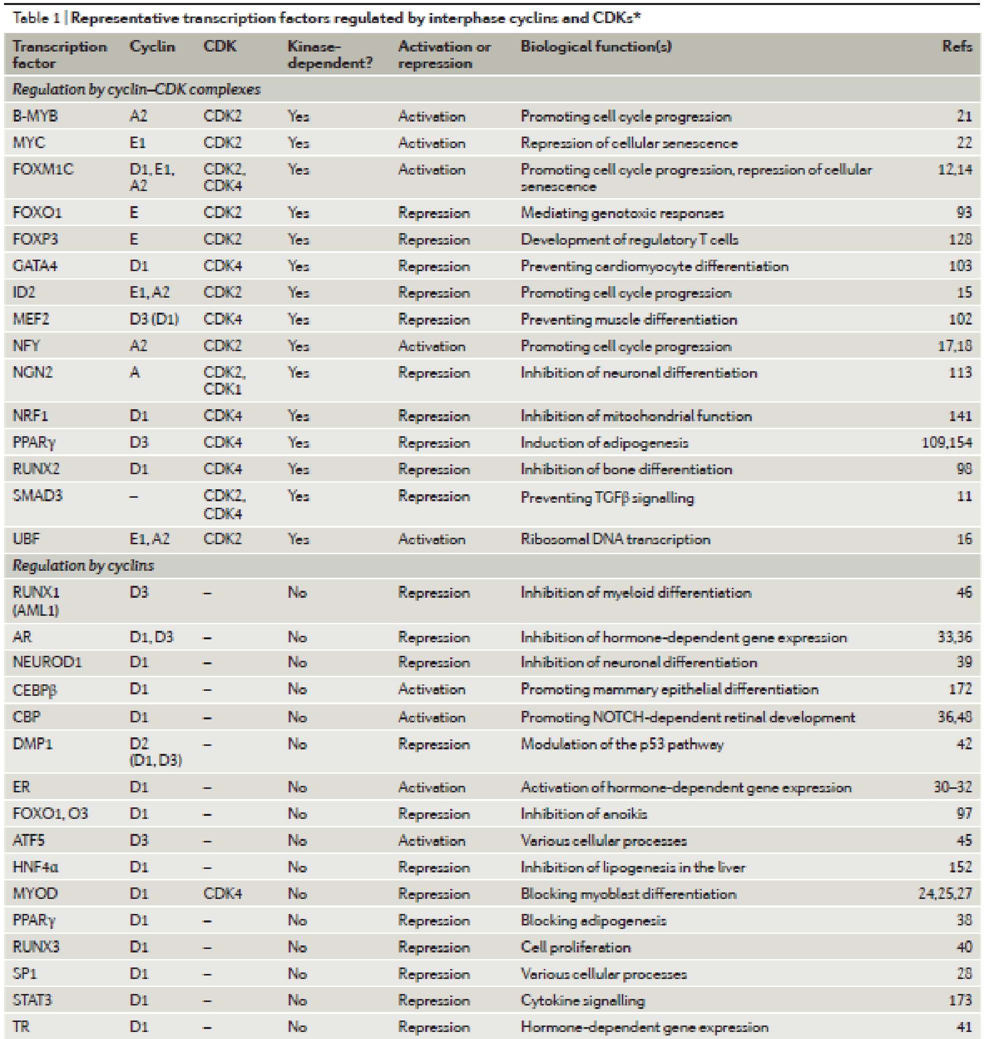


Table 1 | **Representative transcription factors regulated by interphase cyclins and CDKs***

Transcription factor	Cyclin	CDK	Kinase-dependent?	Activation or repression	Biological function(s)	Refs
Regulation by cyclin–CDK complexes						
B-MYB	A2	CDK2	Yes	Activation	Promoting cell cycle progression	21
MYC	E1	CDK2	Yes	Activation	Repression of cellular senescence	22
FOXM1C	D1, E1, A2	CDK2, CDK4	Yes	Activation	Promoting cell cycle progression, repression of cellular senescence	12,14
FOXO1	E	CDK2	Yes	Repression	Mediating genotoxic responses	93
FOXP3	E	CDK2	Yes	Repression	Development of regulatory T cells	128
GATA4	D1	CDK4	Yes	Repression	Preventing cardiomyocyte differentiation	103
ID2	E1, A2	CDK2	Yes	Repression	Promoting cell cycle progression	15
MEF2	D3 (D1)	CDK4	Yes	Repression	Preventing muscle differentiation	102
NFY	A2	CDK2	Yes	Activation	Promoting cell cycle progression	17,18
NGN2	A	CDK2, CDK1	Yes	Repression	Inhibition of neuronal differentiation	113
NRF1	D1	CDK4	Yes	Repression	Inhibition of mitochondrial function	141
PPARγ	D3	CDK4	Yes	Repression	Induction of adipogenesis	109,154
RUNX2	D1	CDK4	Yes	Repression	Inhibition of bone differentiation	98
SMAD3	–	CDK2, CDK4	Yes	Repression	Preventing TGFβ signalling	11
UBF	E1, A2	CDK2	Yes	Activation	Ribosomal DNA transcription	16
Regulation by cyclins						
RUNX1 (AML1)	D3	–	No	Repression	Inhibition of myeloid differentiation	46
AR	D1, D3	–	No	Repression	Inhibition of hormone-dependent gene expression	33,36
NEUROD1	D1	–	No	Repression	Inhibition of neuronal differentiation	39
CEBPβ	D1	–	No	Activation	Promoting mammary epithelial differentiation	172
CBP	D1	–	No	Activation	Promoting NOTCH-dependent retinal development	36,48
DMP1	D2 (D1, D3)	–	No	Repression	Modulation of the p53 pathway	42
ER	D1	–	No	Activation	Activation of hormone-dependent gene expression	30–32
FOXO1, O3	D1	–	No	Repression	Inhibition of anoikis	97
ATF5	D3	–	No	Activation	Various cellular processes	45
HNF4α	D1	–	No	Repression	Inhibition of lipogenesis in the liver	152
MYOD	D1	CDK4	No	Repression	Blocking myoblast differentiation	24,25,27
PPARγ	D1	–	No	Repression	Blocking adipogenesis	38
RUNX3	D1	–	No	Repression	Cell proliferation	40
SP1	D1	–	No	Repression	Various cellular processes	28
STAT3	D1	–	No	Repression	Cytokine signalling	173
TR	D1	–	No	Repression	Hormone-dependent gene expression	41

Plant Molecular Biology **43:** 607–620, 2000.
Dirk Inzé (Ed.), The Plant Cell Cycle.
© 2000 *Kluwer Academic Publishers. Printed in the Netherlands.*

CDK-related protein kinases in plants

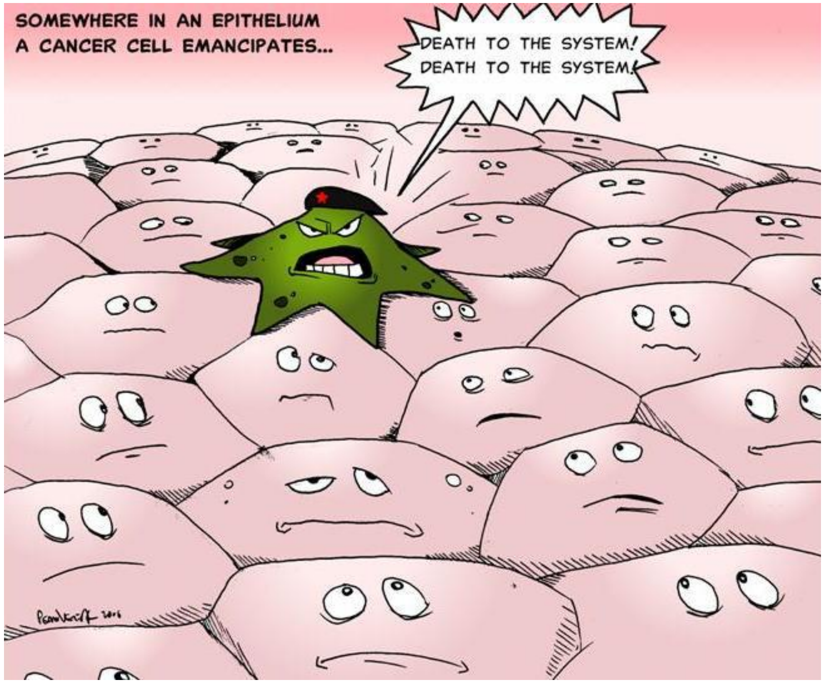
Plant Cell Physiol. 46(9): 1437–1442 (2005)
doi:10.1093/pcp/pci170, available online at www.pcp.oupjournals.org
JSPP © 2005

Mini Review

Control of Cell Division and Transcription by Cyclin-dependent Kinase-activating Kinases in Plants

Masaaki Umeda [1, *], Akie Shimotohno and Masatoshi Yamaguchi
Institute of Molecular and Cellular Biosciences, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo, 113-0032 Japan

Aula 14/06 – RNAi e mecanimso de regulação e suas aplicações biotecnológicas.


SOMEWHERE IN AN EPITHELIUM
A CANCER CELL EMANCIPATES...
DEATH TO THE SYSTEM!
DEATH TO THE SYSTEM!