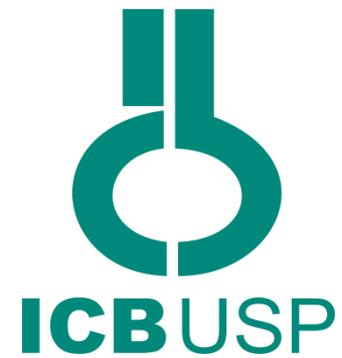




DEPARTAMENTO DE  
**MICroBiologia**  
UNIVERSIDADE DE SÃO PAULO



# Ciclo Celular

**Enrique Boccardo**

Departmento de Microbiologia

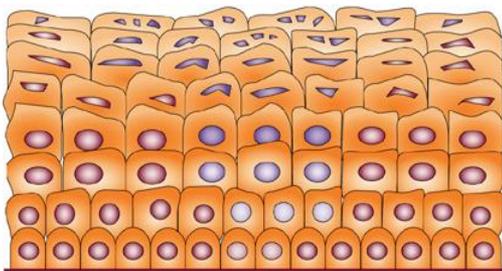
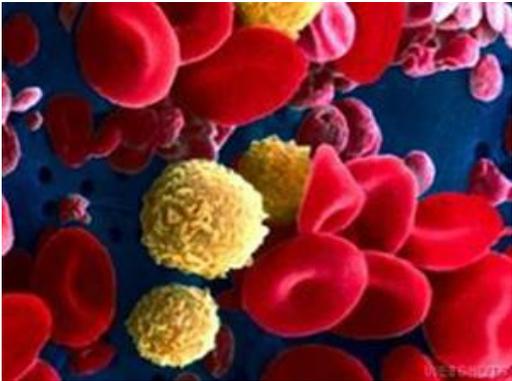
ICB/USP

[eboccardo@usp.br](mailto:eboccardo@usp.br)

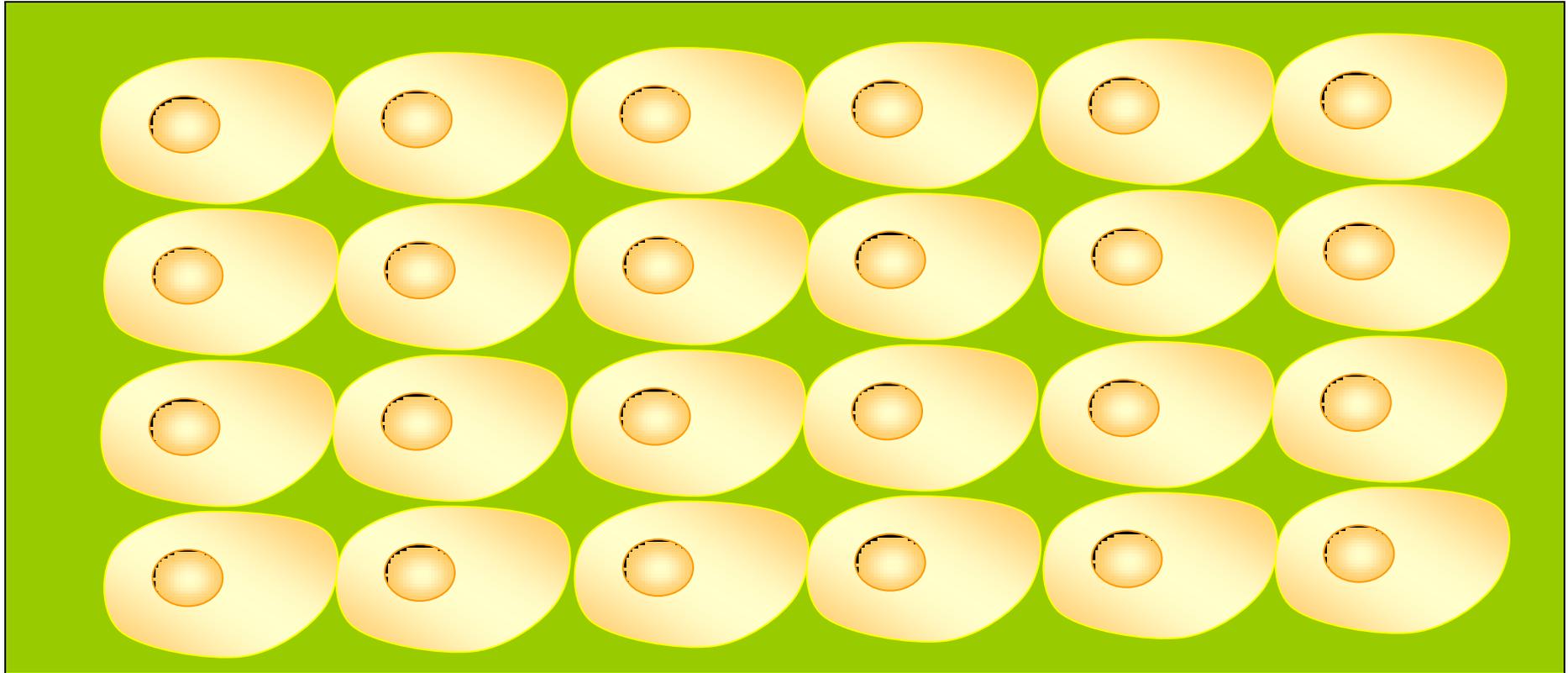
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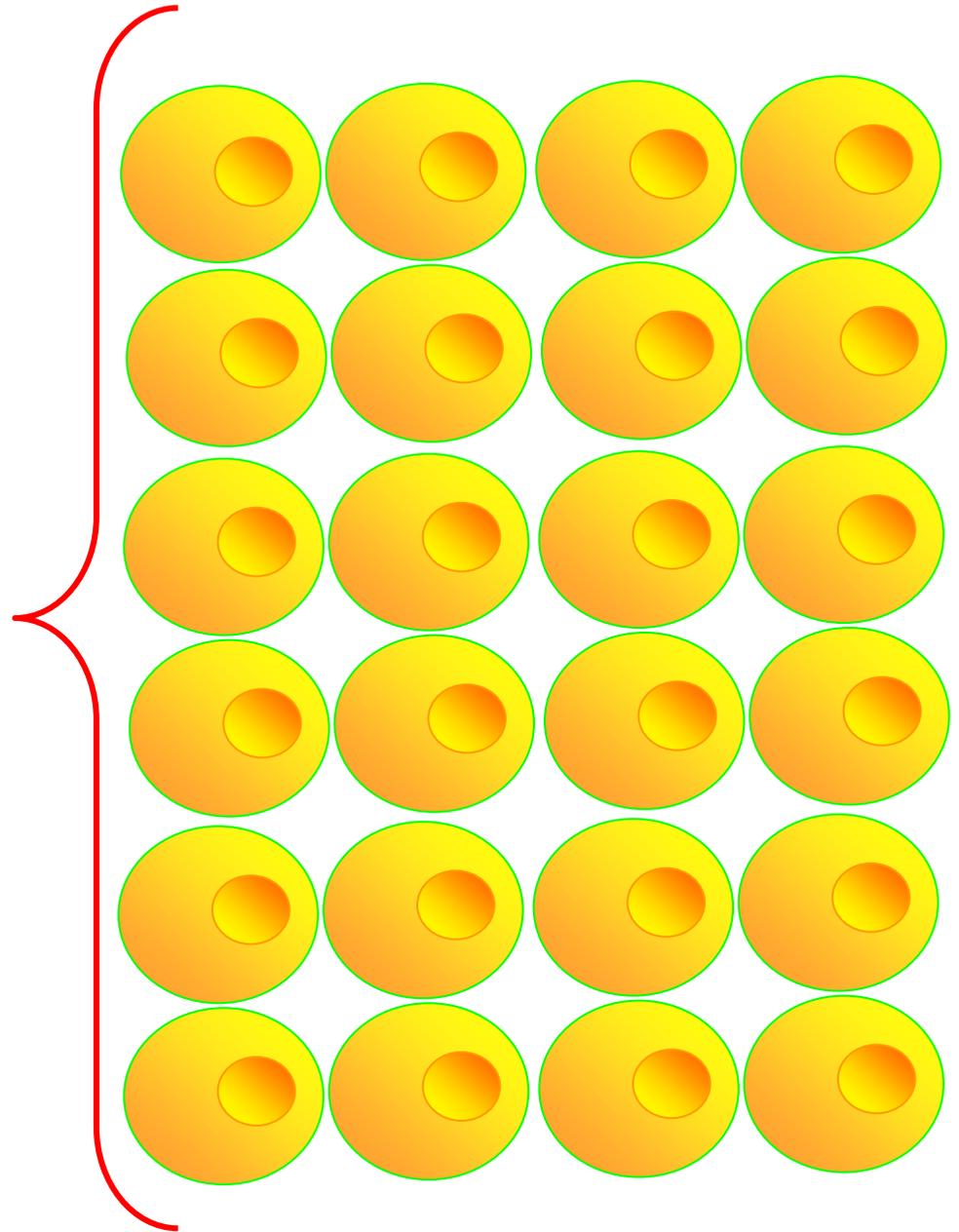
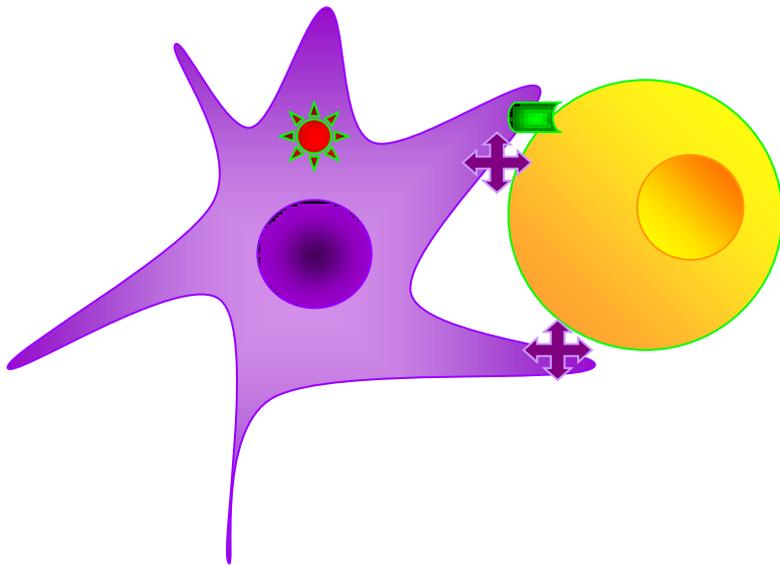
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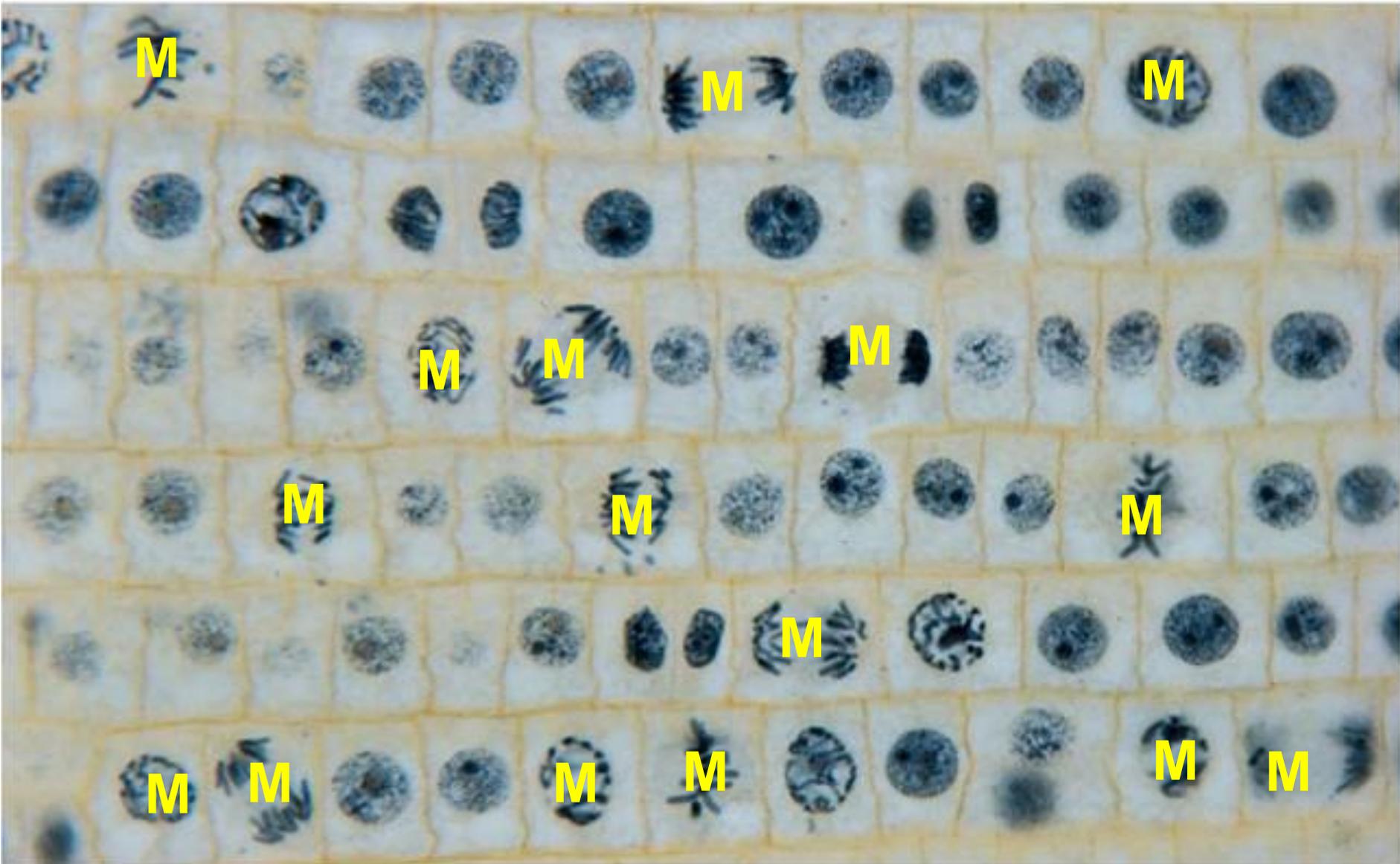
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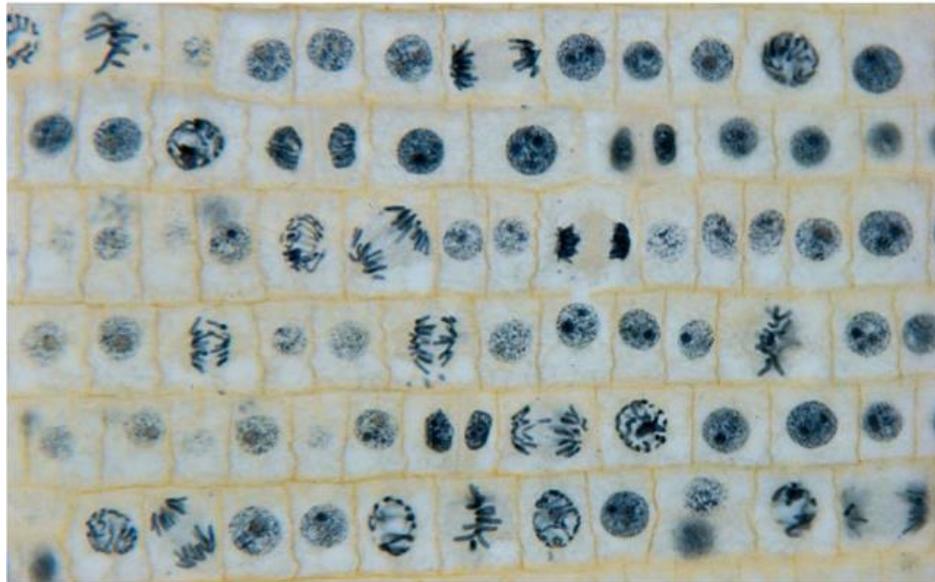
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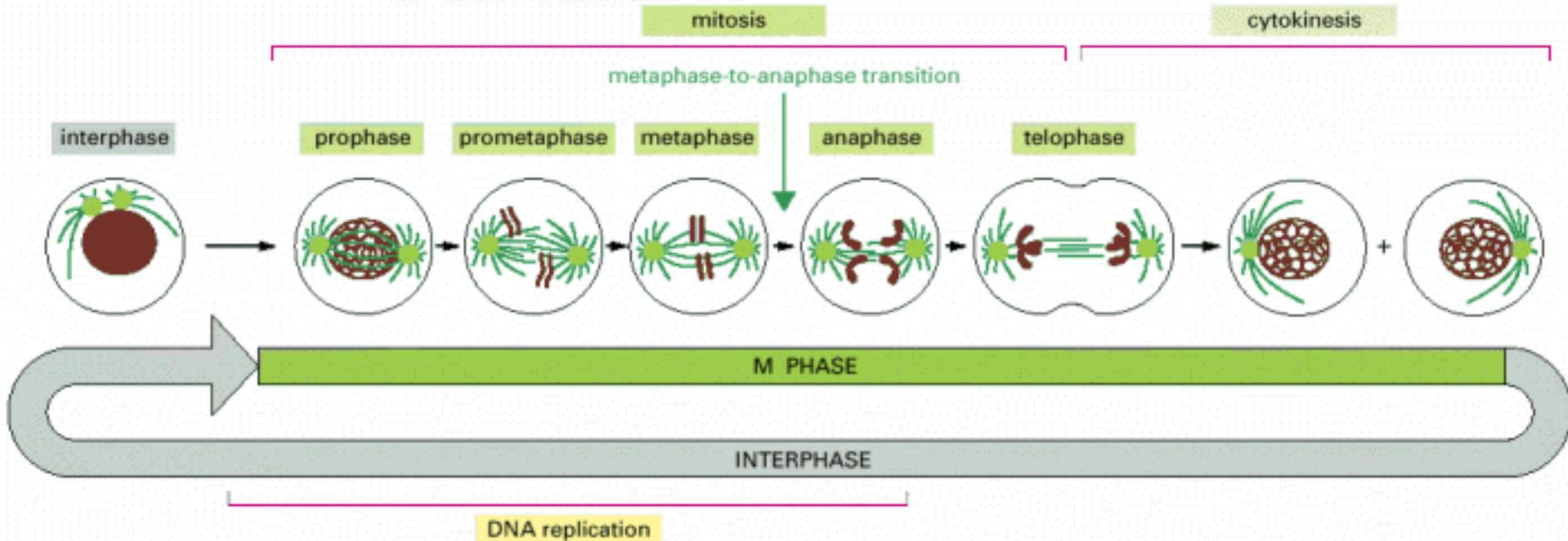
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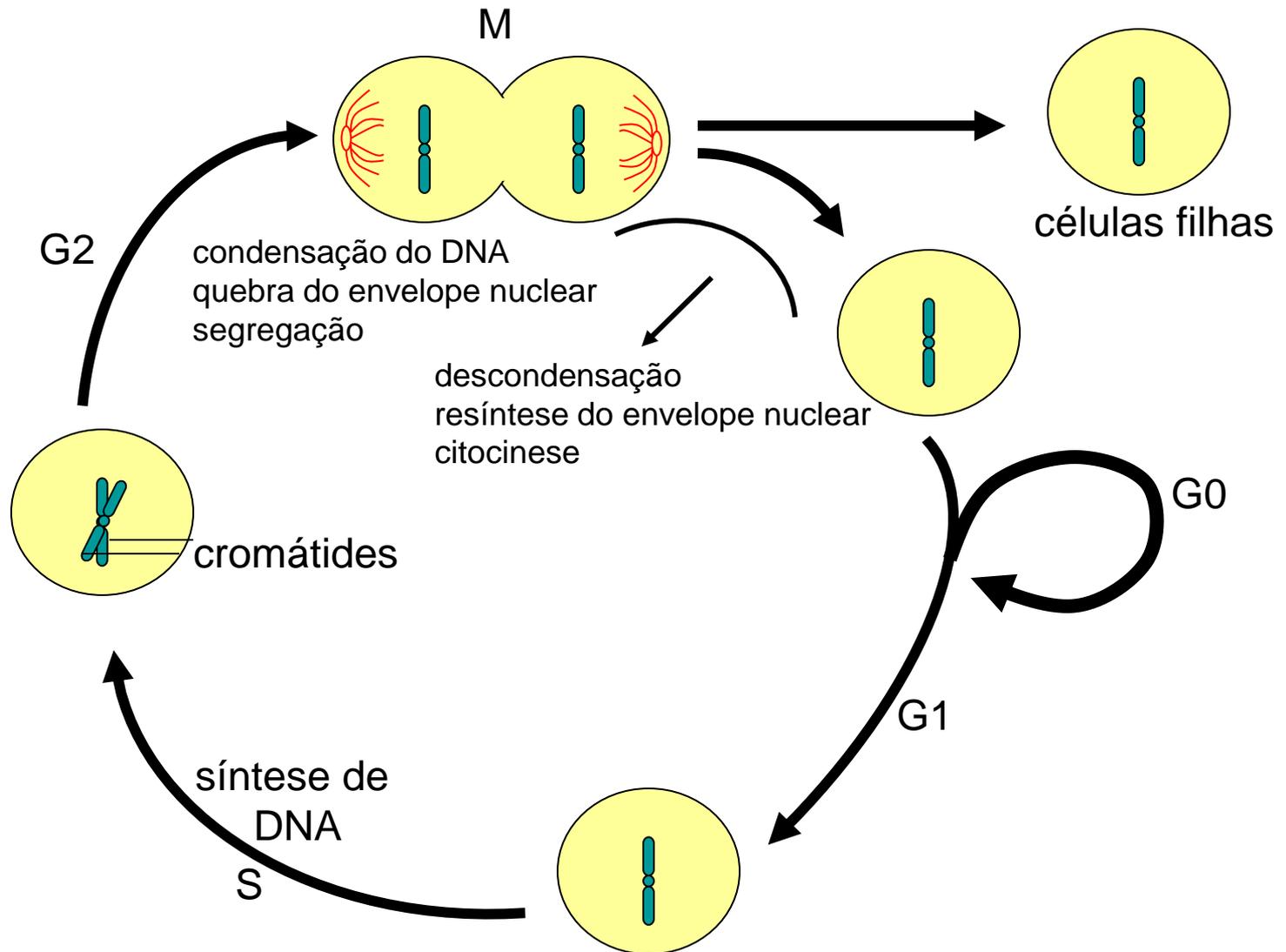
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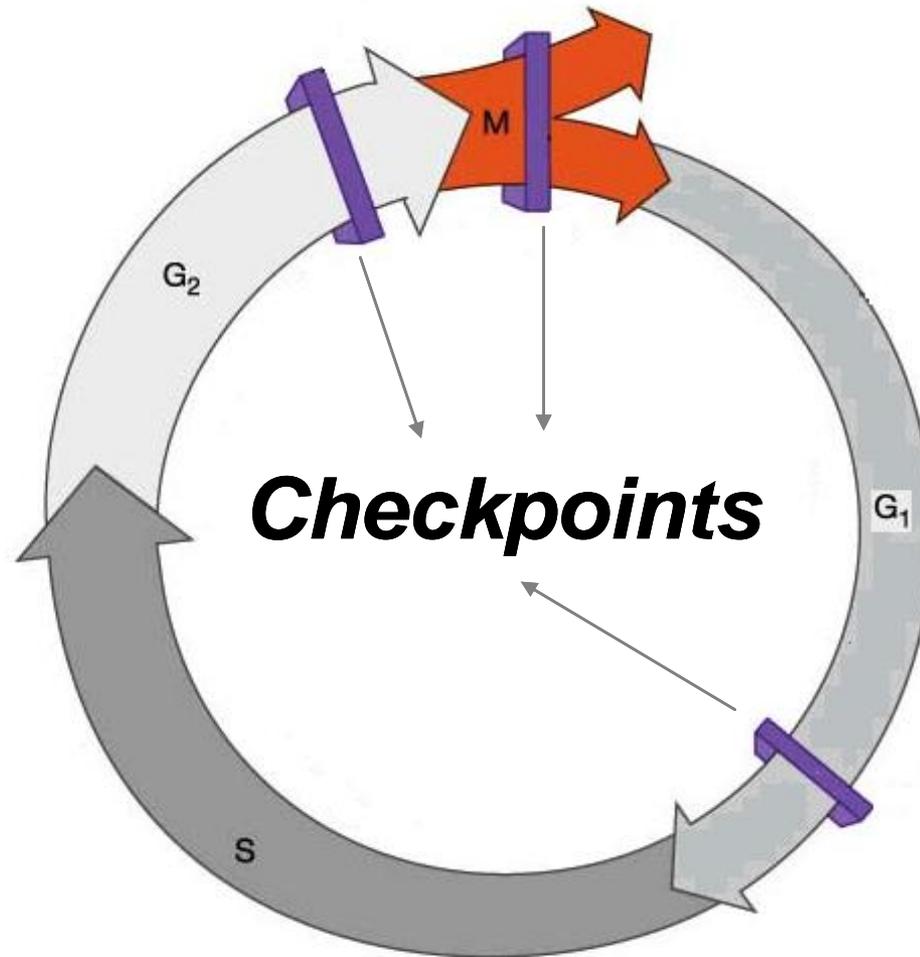
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# Ciclo celular



# Ciclo celular



# Ciclo celular

## G2-M Transition

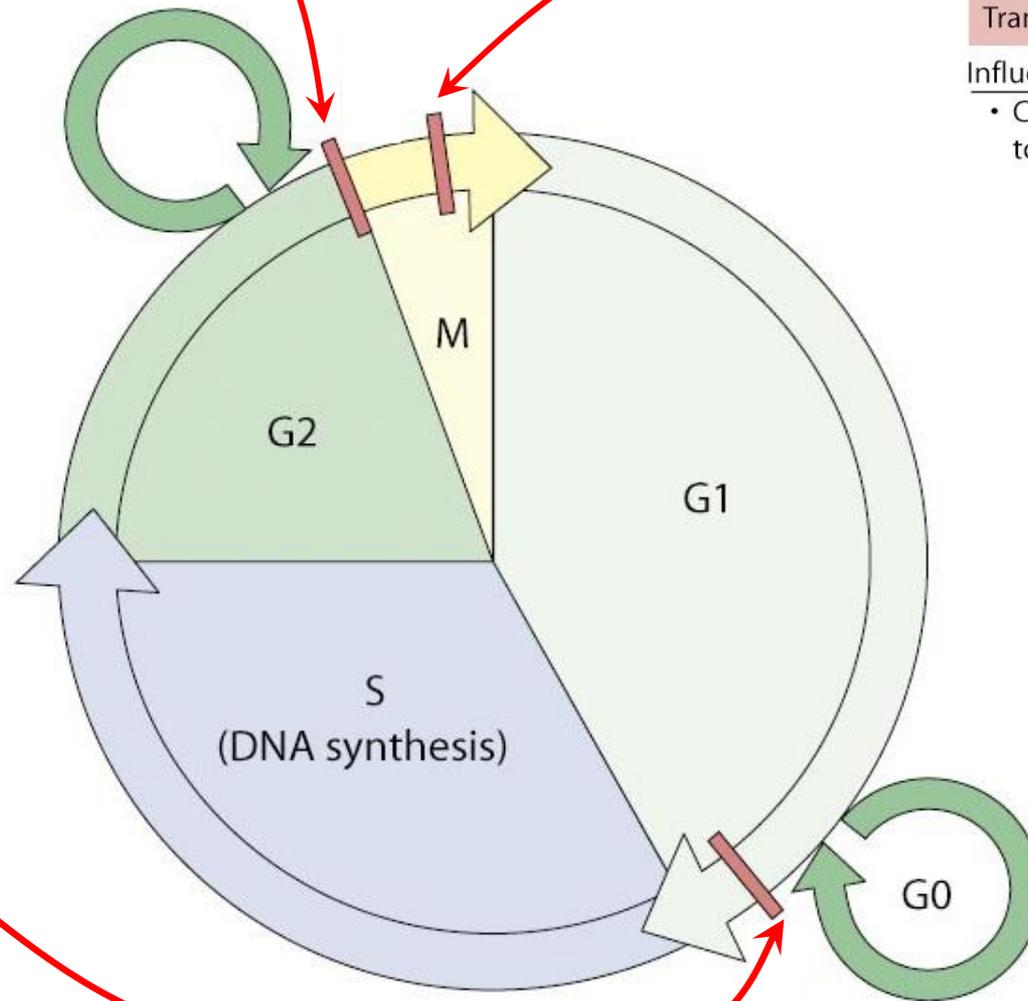
Influenced by:

- Cell size
- DNA damage
- DNA replication

## Metaphase-Anaphase Transition

Influenced by:

- Chromosome attachments to spindle

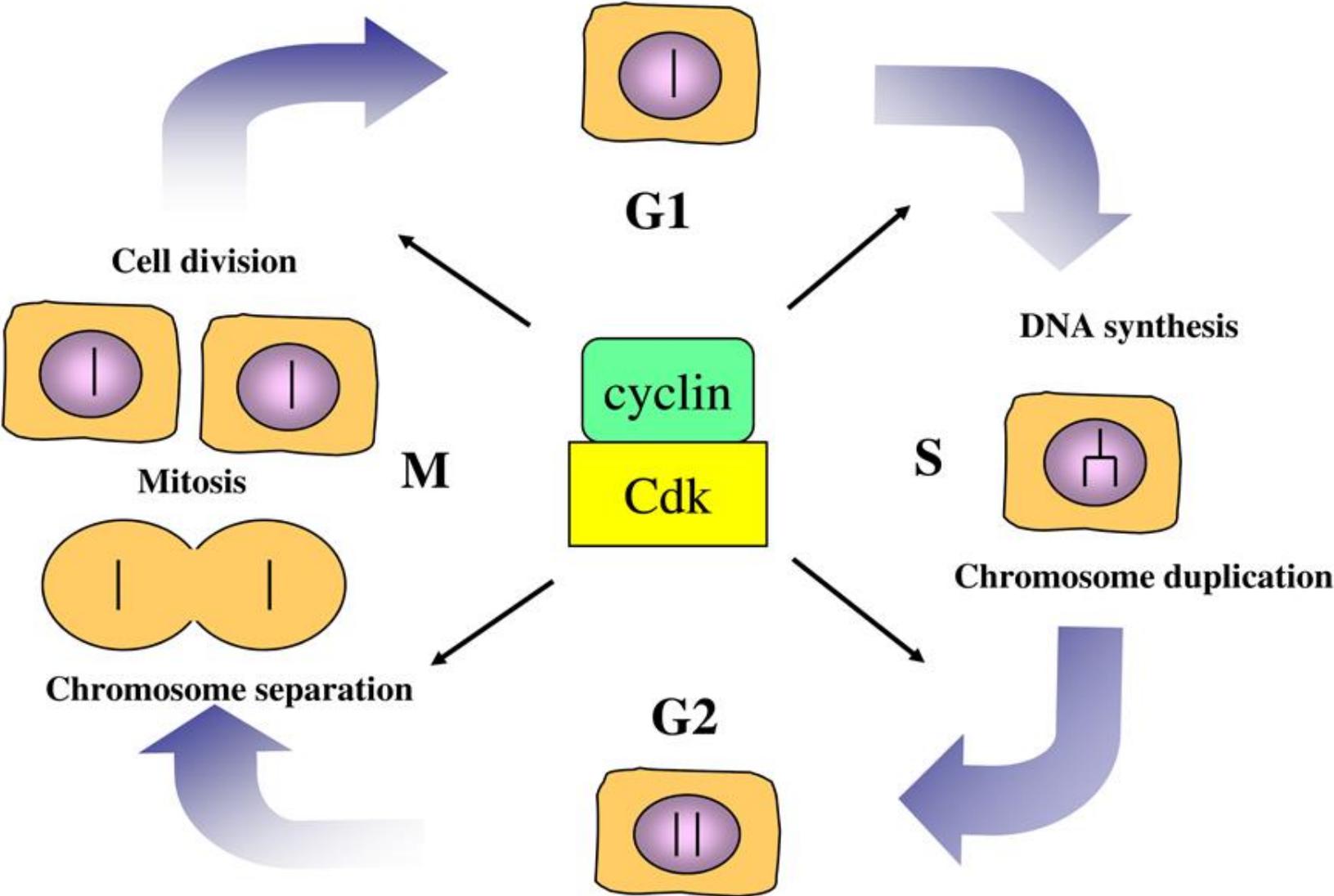


## Restriction Point (Start)

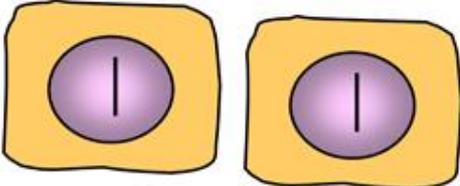
Influenced by:

- Growth factors
- Nutrients
- Cell size
- DNA damage

# Ciclo celular

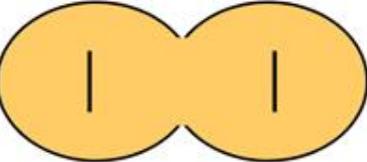


Cell division



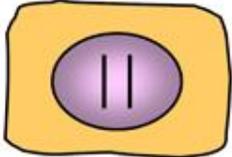
Mitosis

M



Chromosome separation

G2

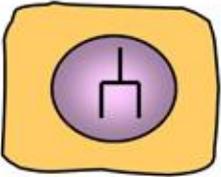


G1

cyclin  
Cdk

DNA synthesis

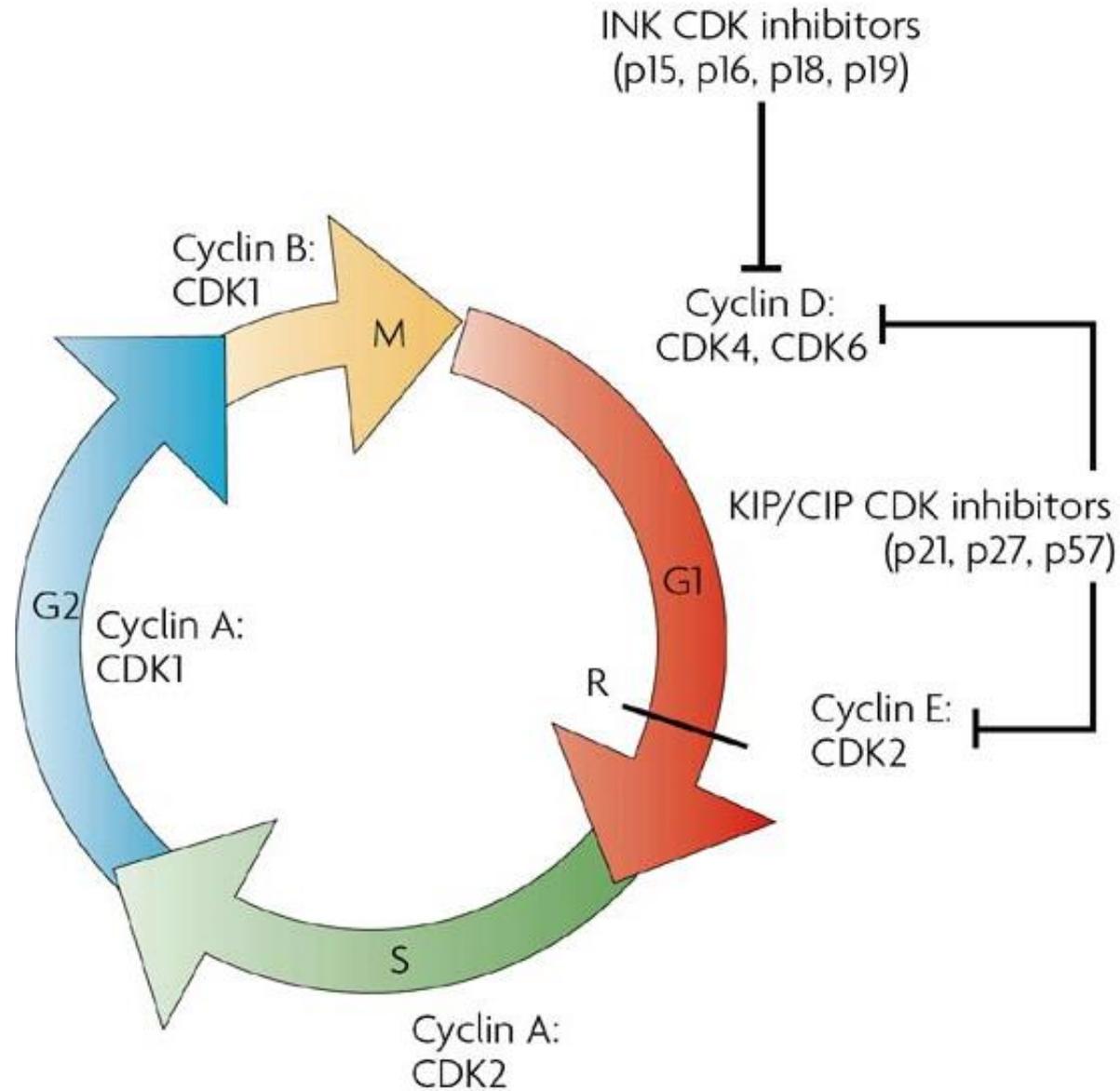
S



Chromosome duplication

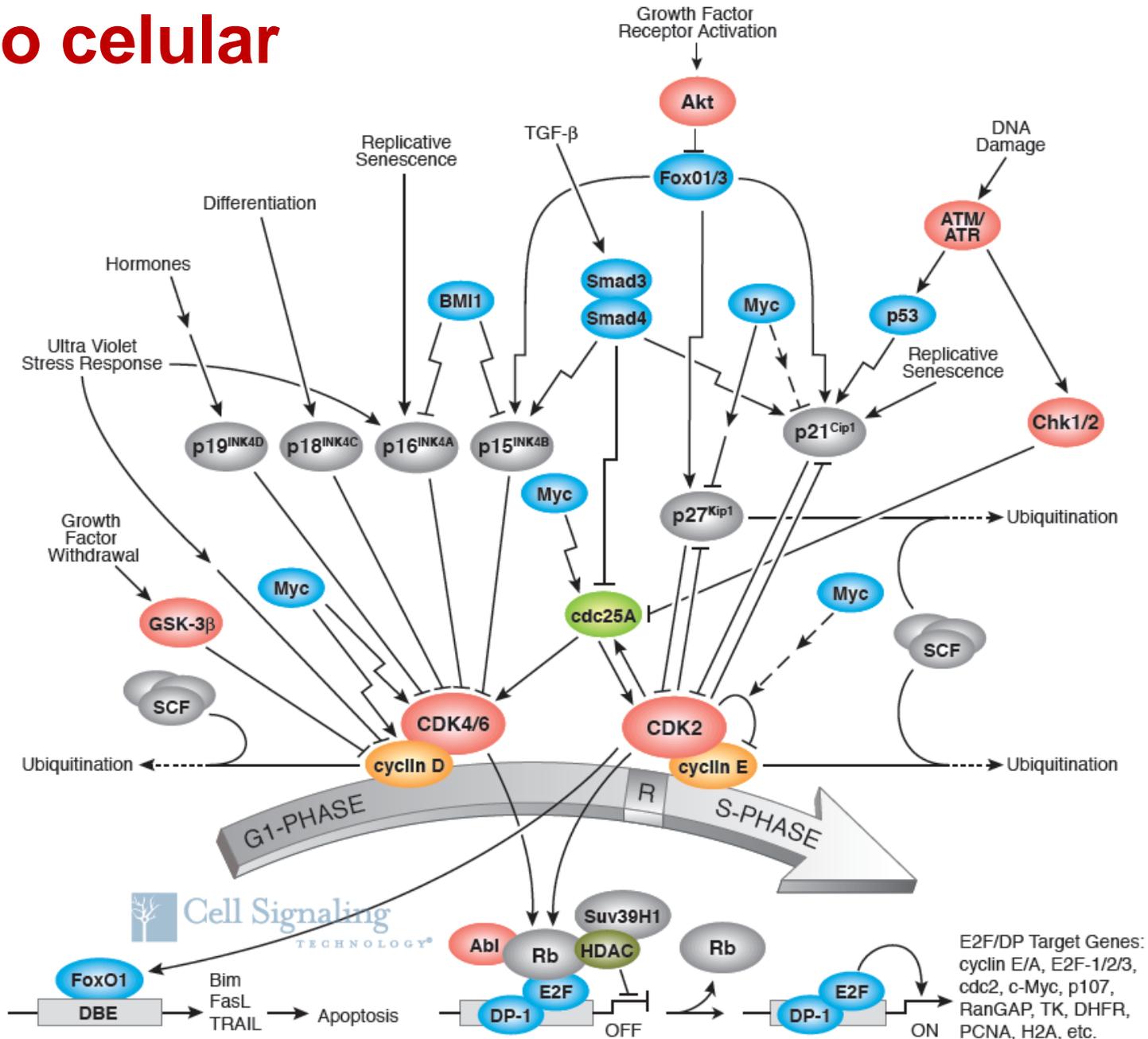
Cells with duplicated chromosomes

# Ciclo celular



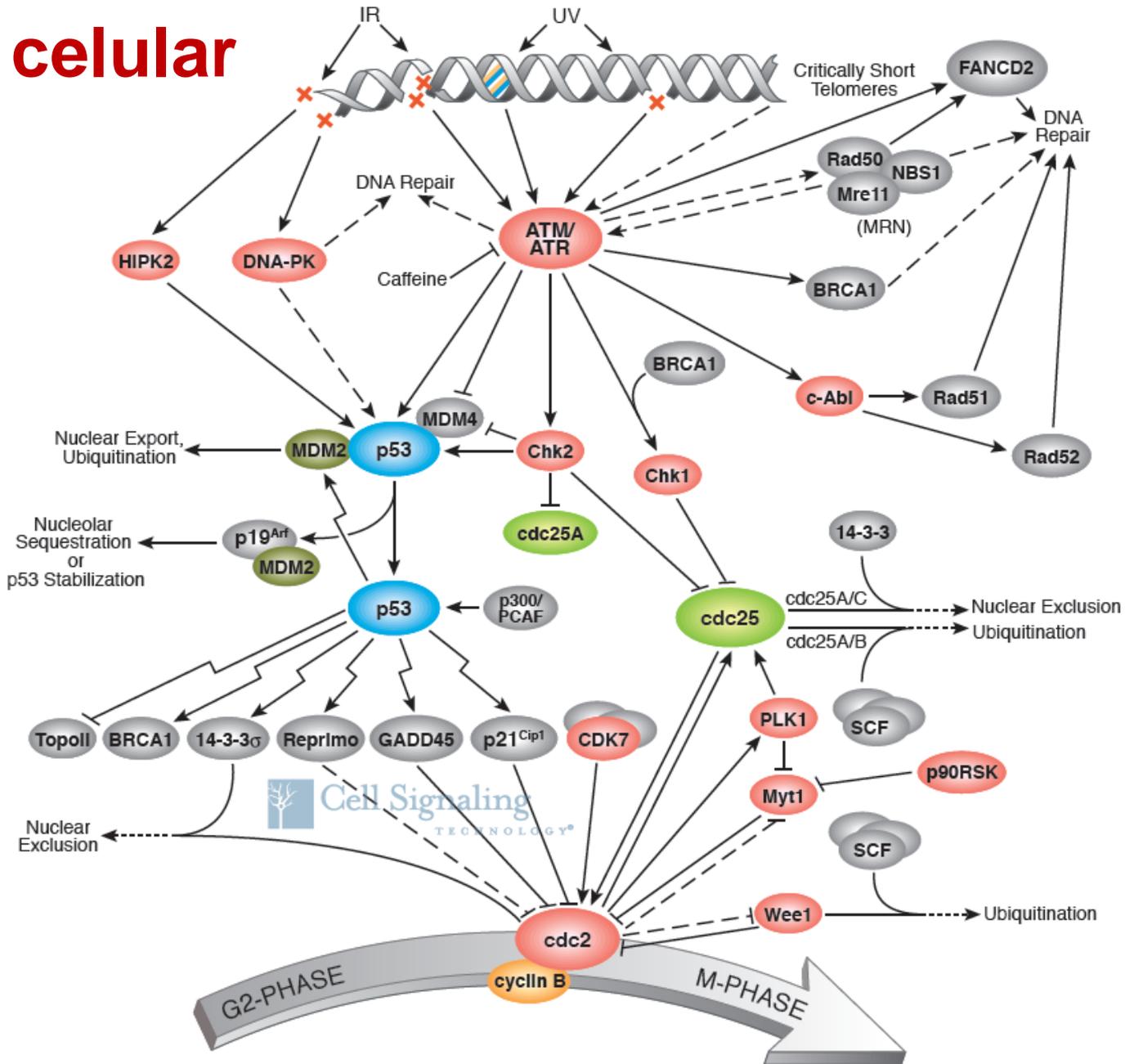
# Cell Cycle Control: G1/S Checkpoint

## Ciclo celular



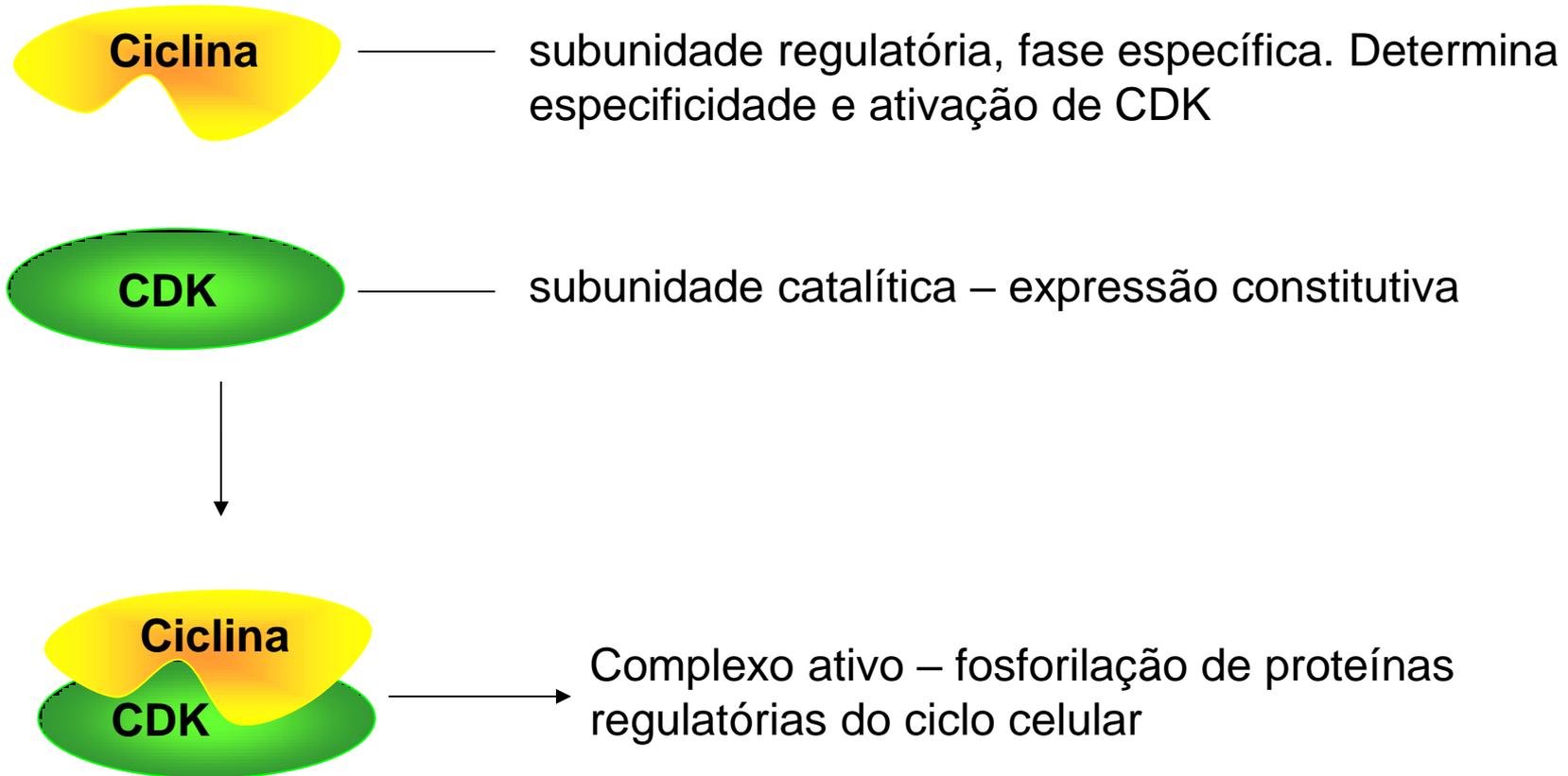
# Cell Cycle Control: G2/M DNA Damage Checkpoint

## Ciclo celular



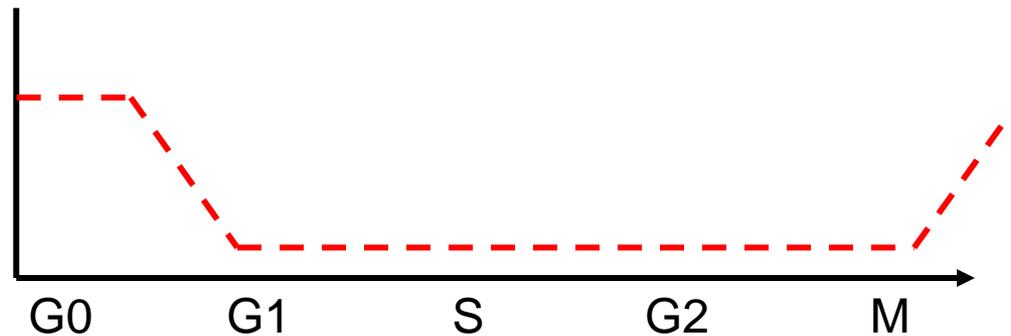
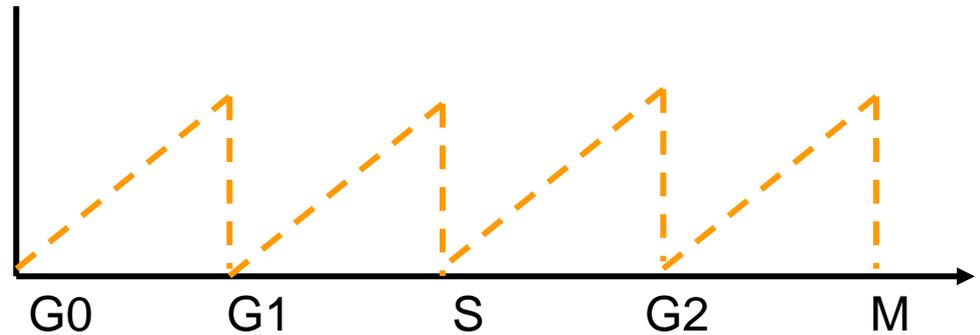
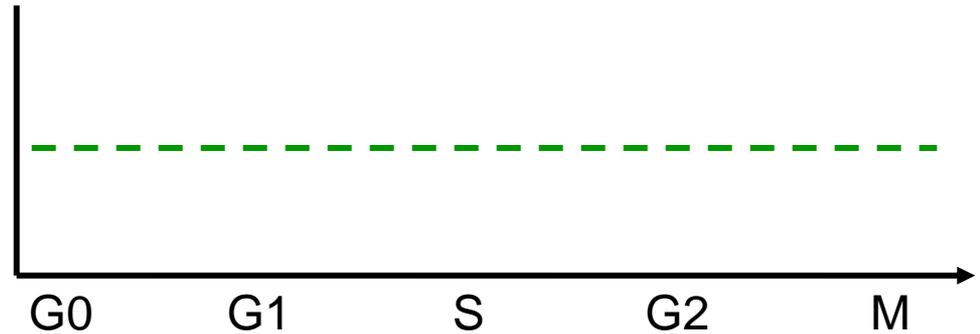
# Ciclo celular

## Controladores do ciclo celular

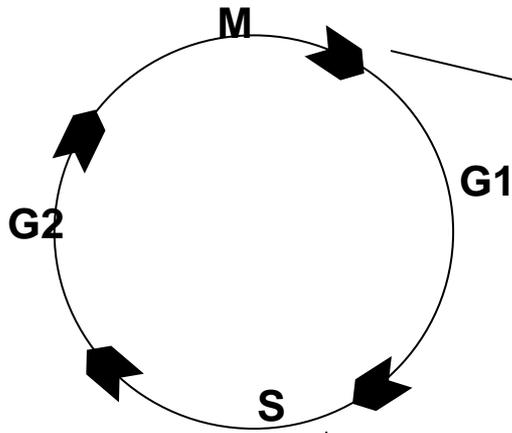


# Ciclo celular

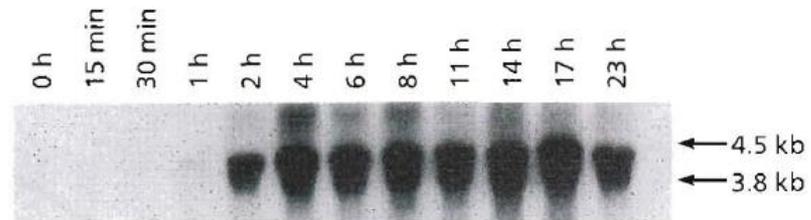
## Regulação da atividade dos complexos ciclina/CDK



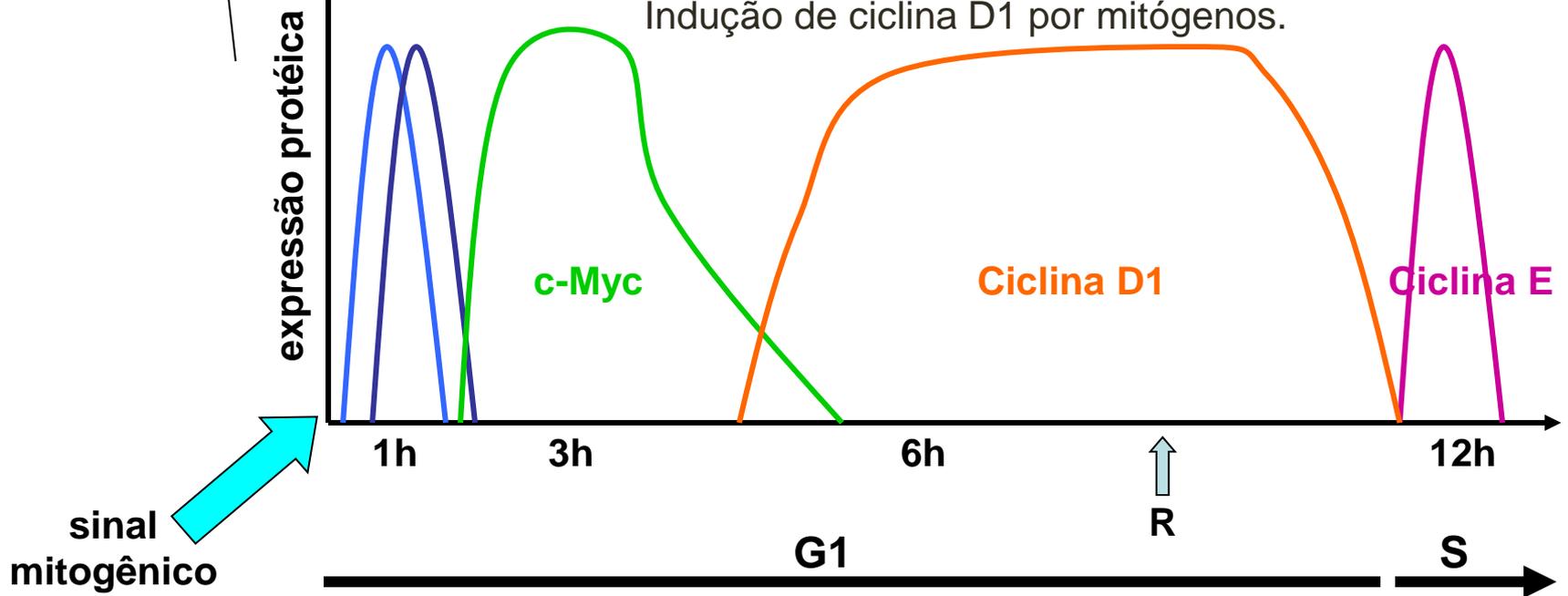
# Ciclo celular



## Controle/expressão fase-específico



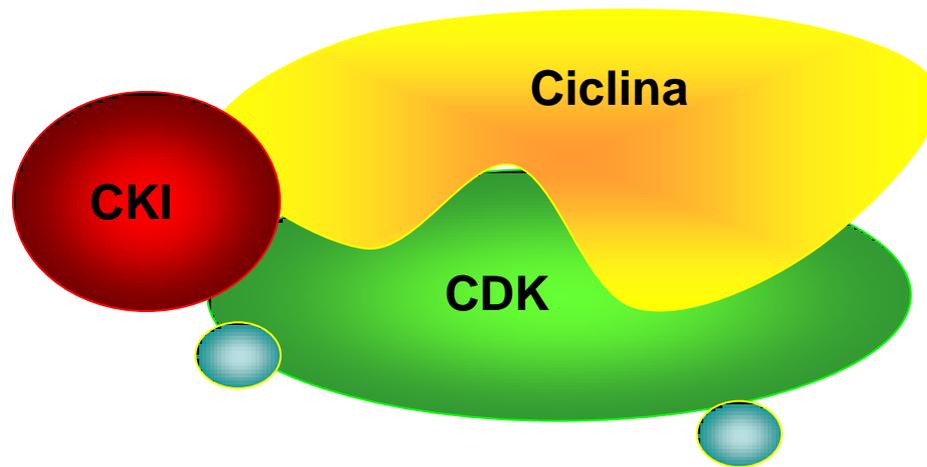
Indução de ciclina D1 por mitógenos.



# Ciclo celular

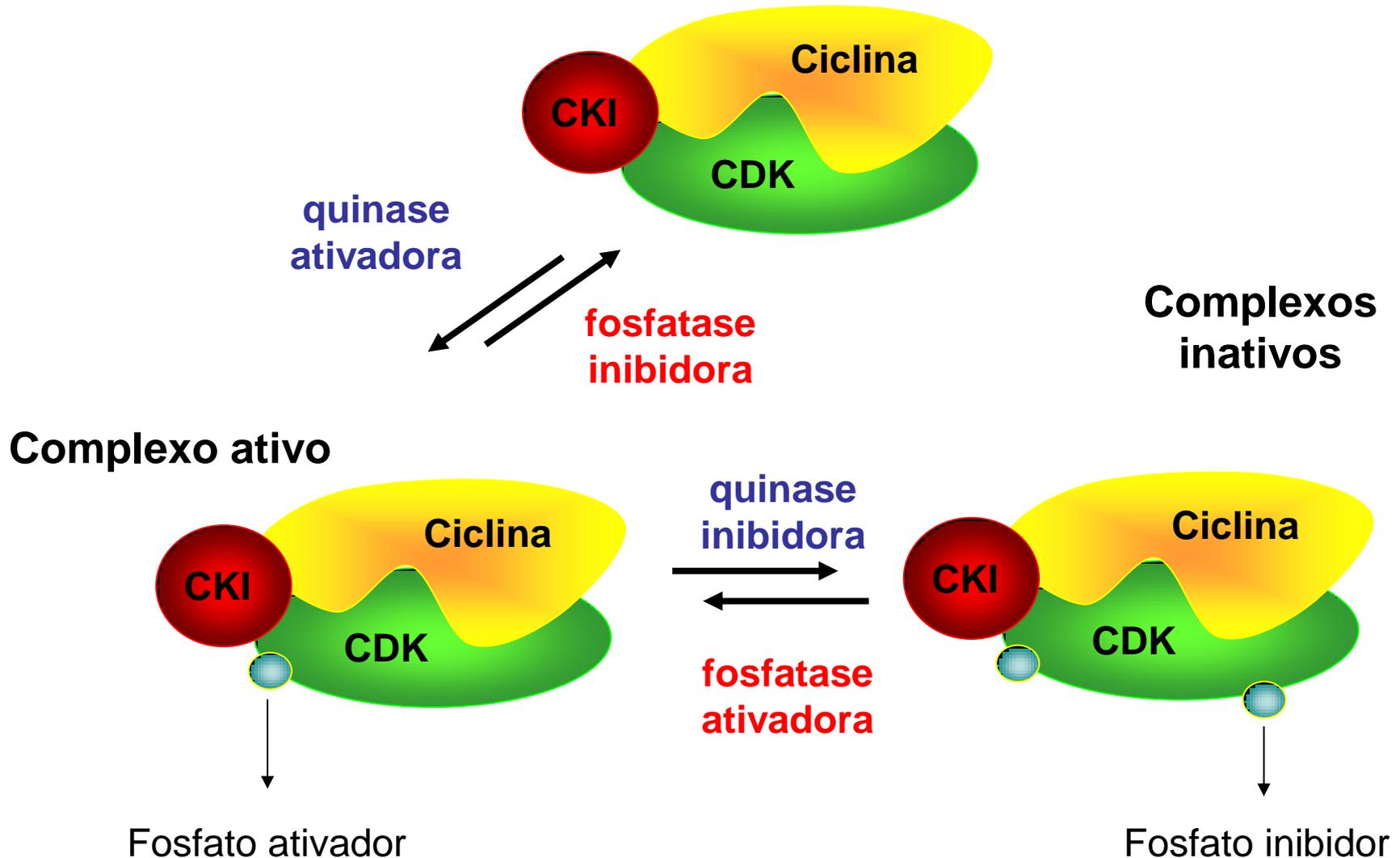
Regulação da atividade dos complexos ciclina/CDK...

Uma tarefa nada simples...



# Ciclo celular

Regulação da atividade dos complexos ciclina/CDK



# Ciclo celular

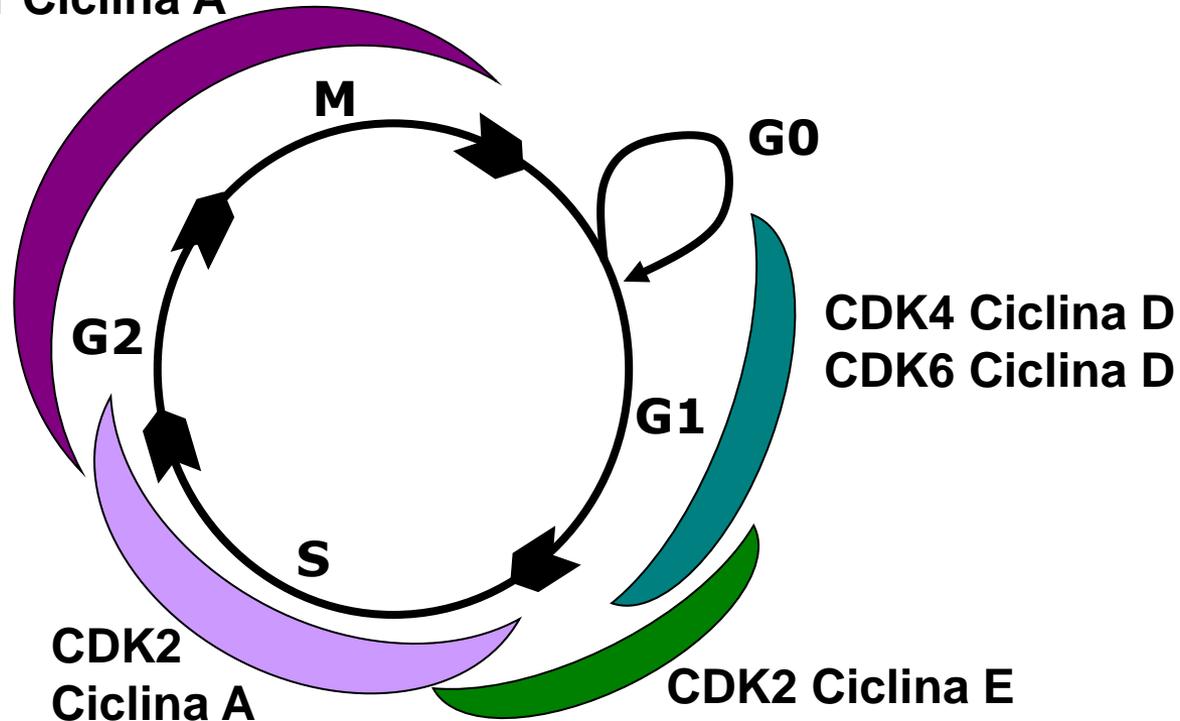
## CDK, Ciclinas e fases do ciclo

CDK1	Ciclinas A, B	G2/M
CDK2	Ciclinas A, E	G1/S, S
CDK3	Ciclina E	G1/S
CDK4	Ciclina D	G1/S
CDK5	Ciclina D	Diferenciação neuronal
CDK6	Ciclina D	G1/S
CDK7	Ciclina H	CAK (CDK activating kinase)
CDK8	Ciclina C	Regulação transcricional
CDK9	Ciclina T	G1/S

# Ciclo celular

Controle/expressão fase-específico

CDK1 Ciclina B  
CDK1 Ciclina A



# Ciclo celular

## CDK, Ciclinas e CKI

CDK1

Ciclinas A, B

p27, p21, p57

CDK2

Ciclinas A, E

p27, p21, p57

CDK3

Ciclina E

CDK4

Ciclina D

p15, p16, p18, p19

CDK5

Ciclina D

p15, p16, p18, p19

CDK6

Ciclina D

p15, p16, p18, p19

CDK7

Ciclina H

CDK8

Ciclina C

CDK9

Ciclina T

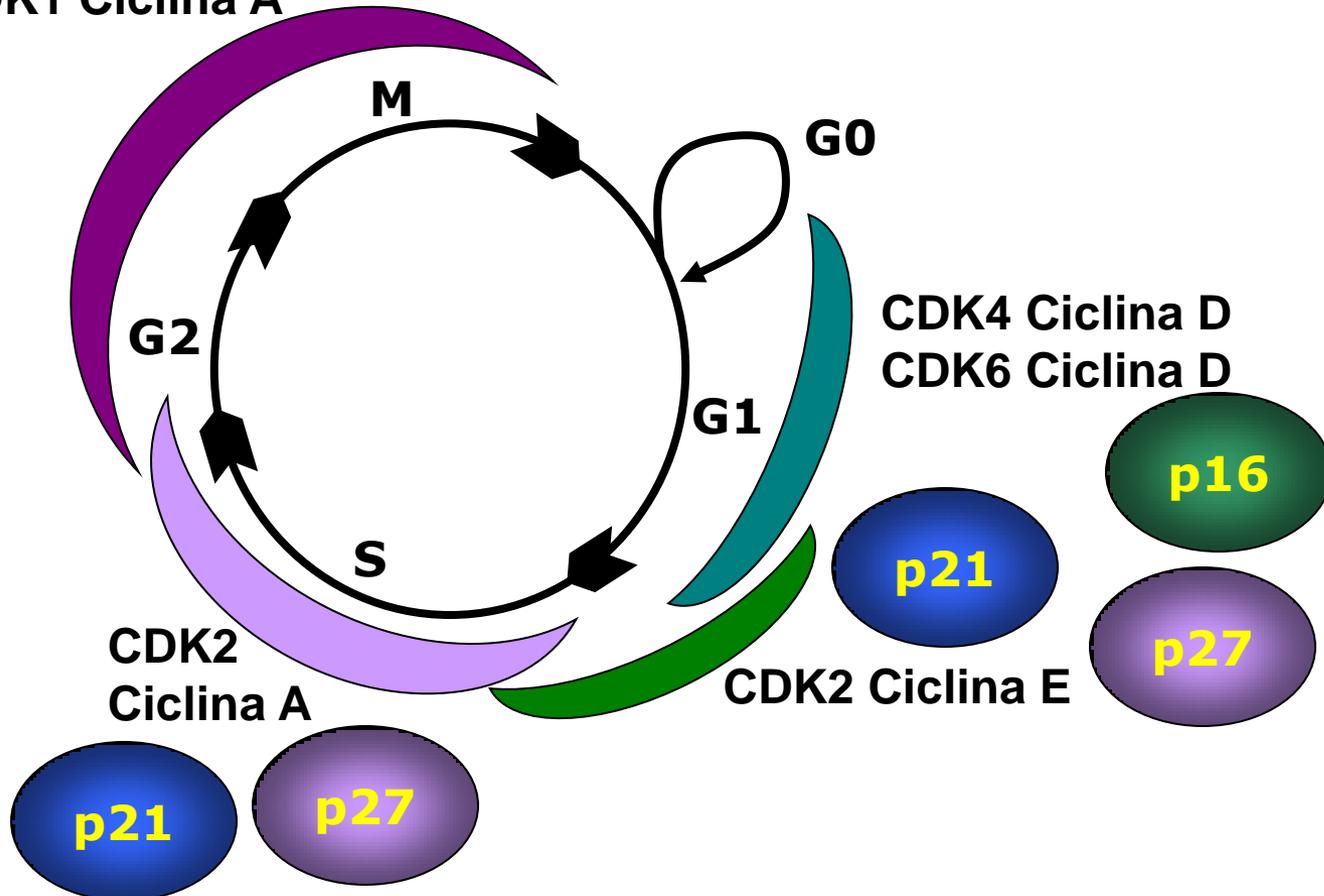
cip/kip

INK4

# Ciclo celular

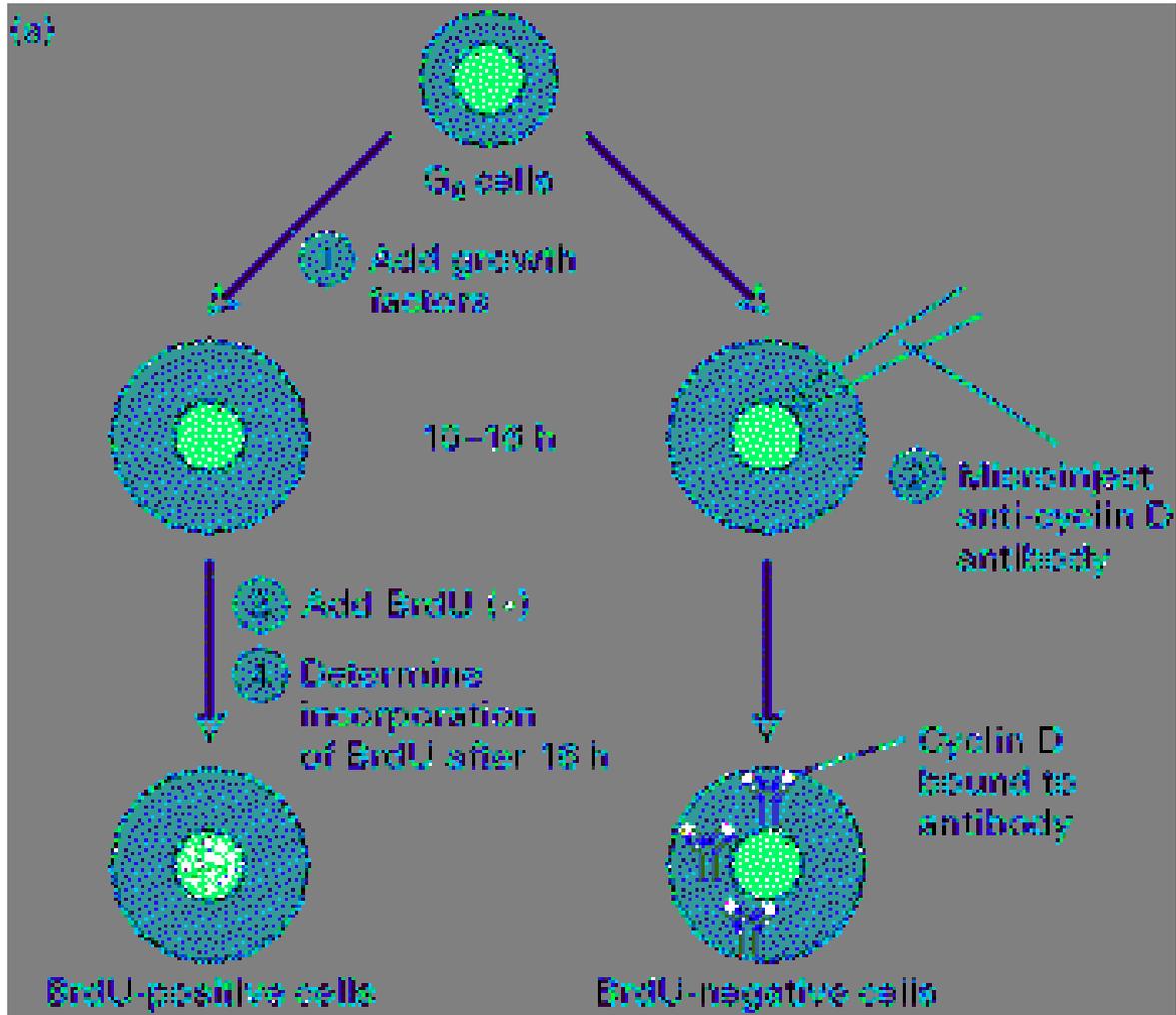
## CDK, Ciclinas e CKI

CDK1 Ciclina B  
CDK1 Ciclina A



# Ciclo celular

## FUNÇÃO: exemplo da ciclina D



### Ciclina D:

Importante na progressão do ciclo devido à sua interação com p21 e p27

# Ciclo celular

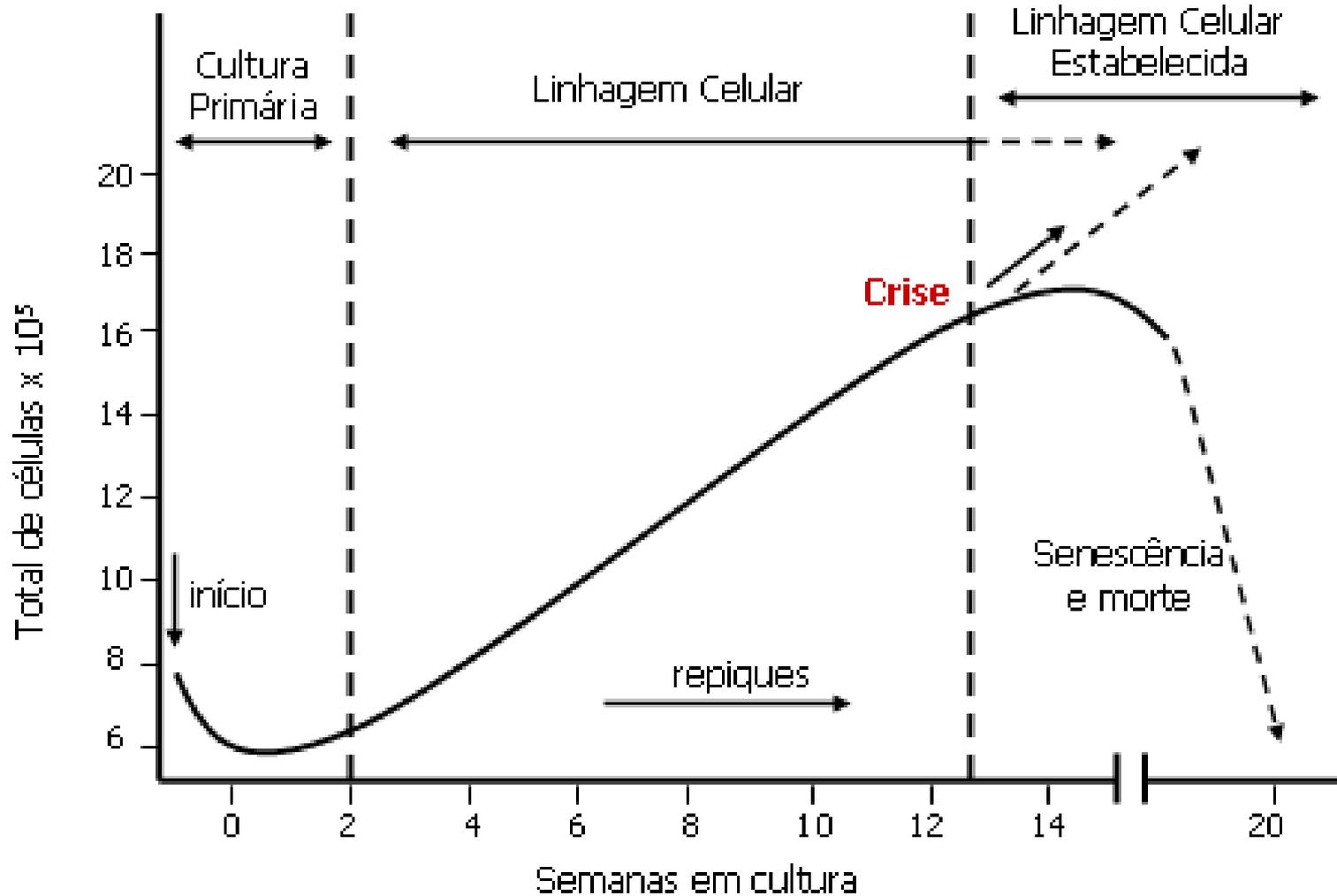
## Resumo: Principais funções das ciclinas

- Ciclinas D** – fosforilação de pRb levando à expressão de genes, cujos produtos são necessários para a síntese de DNA, controle da expressão de *ciclina E*
- Ciclina E** – mantém pRb fosforilada, importante para a progressão de G1 e na transição G1/S (pode substituir a Ciclina D), regula a transcrição de genes de histonas e o início da replicação do DNA
- Ciclina A** – fosforila proteínas regulatórias do complexo de pré-iniciação de replicação ativando a mesma e impedindo a formação de novos complexos de pré-iniciação. Importante nas transições G1/S e G2/M
- Ciclina B** – condensação do DNA genômico, ativação de APC que degrada o inibidor de anáfase e também inicia a telófase

# Perda do controle do **Ciclo celular**

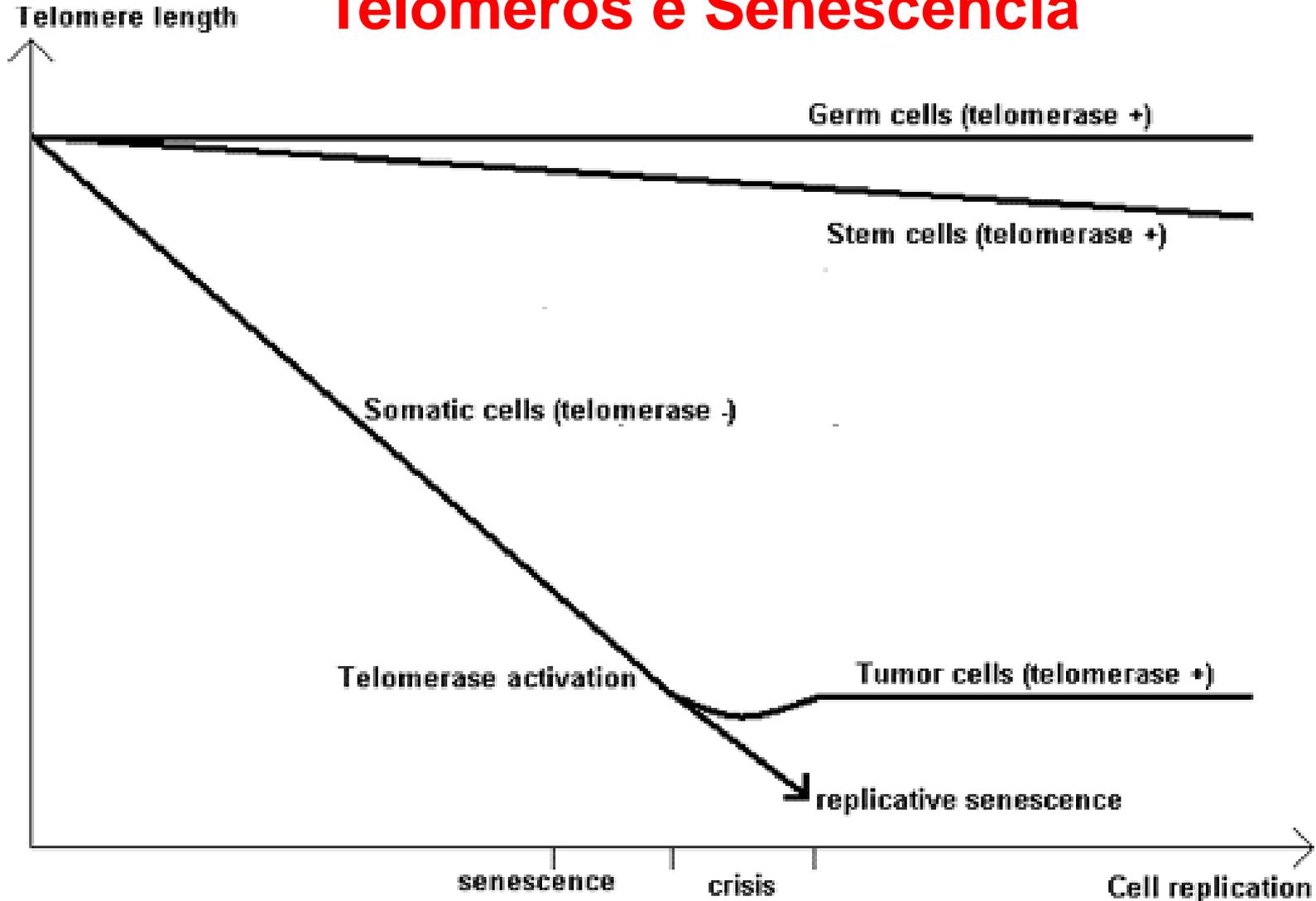
- **Imortalização e transformação celular**

# Ciclo celular: Imortalização e transformação



# Ciclo celular: Imortalização e transformação

## Telômeros e Senescência



# **Ciclo celular: Imortalização e transformação**

	<b>Célula normal</b>
<b>Capacidade replicativa</b>	Limitada
<b>Inibição por contato</b>	Sim
<b>Densidade de saturação</b>	Baixa
<b>Dependência de fatores de crescimento</b>	Alta
<b>Crescimento independente de substrato</b>	Não
<b>Formação de tumores em camundongos nude</b>	Não

# Perda do controle do **Ciclo celular**

- **Oncogenes e genes supressores de Tumor**

# Perda do controle do **Ciclo celular**

## Proto-oncogenes

### Definição clássica

- Genes celulares normais.
- Os produtos dos proto-oncogenes estão envolvidos na regulação da progressão do ciclo celular.
- As mutações nestes genes são dominantes

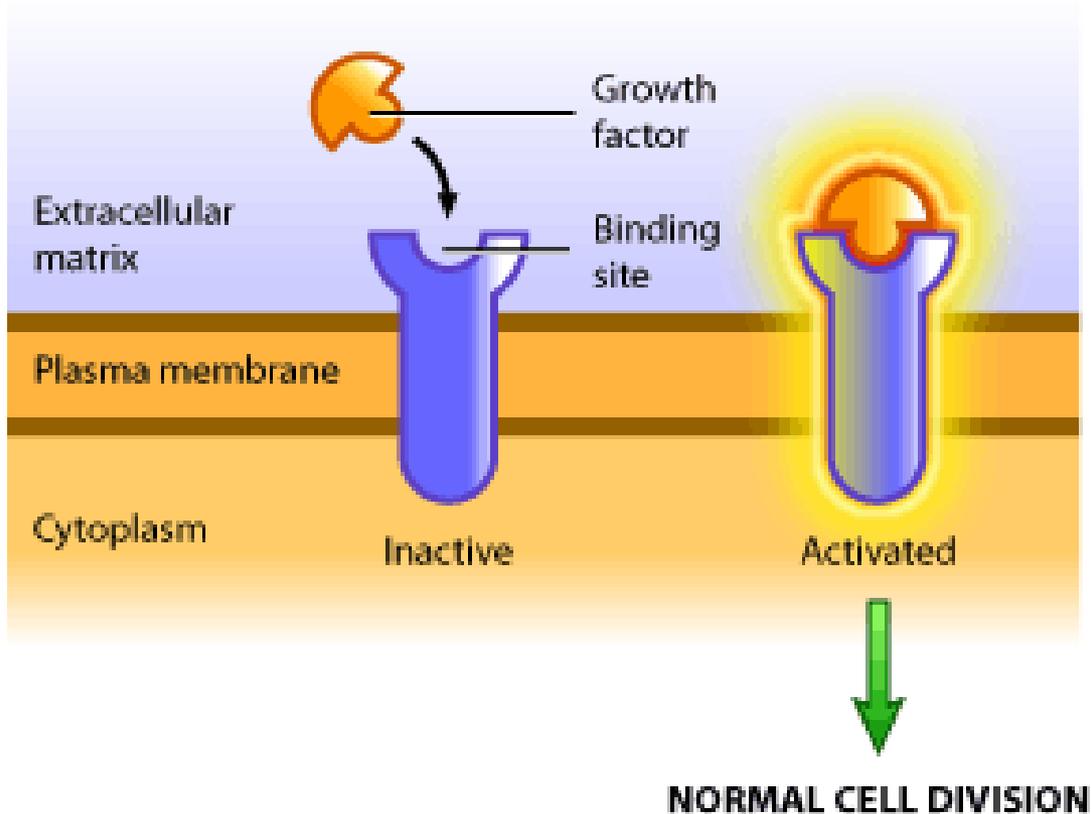
# Perda do controle do **Ciclo celular**

## Os proto-oncogenes codificam:

- Fatores de crescimento
- Receptores de fatores de crescimento
- Proteínas G
- Proteínas citoplasmáticas envolvidas na transdução de sinal
- Fatores de transcrição

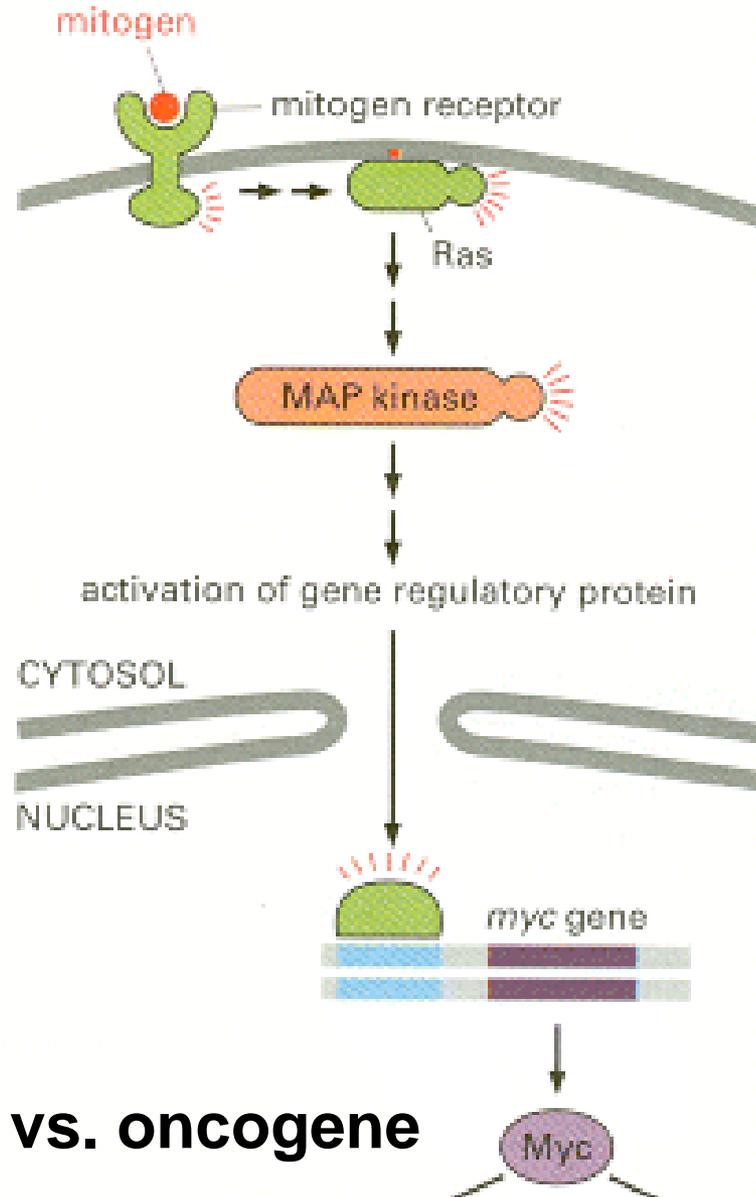
# Perda do controle do **Ciclo celular**

## Proto-oncogene vs. oncogene



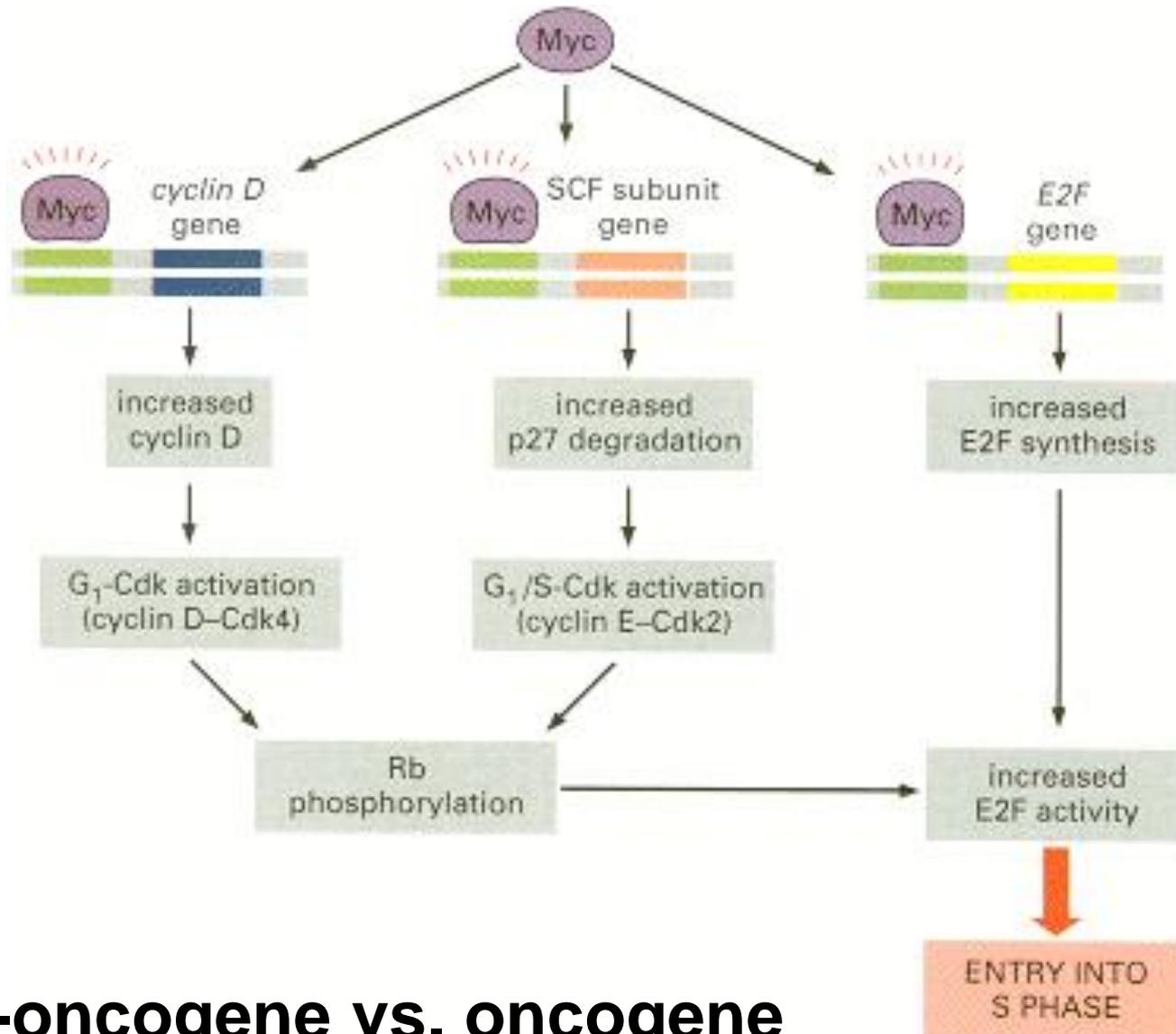
Como um proto-oncogene vira um oncogene?

# Perda do controle do **Ciclo celular**



**Proto-oncogene vs. oncogene**

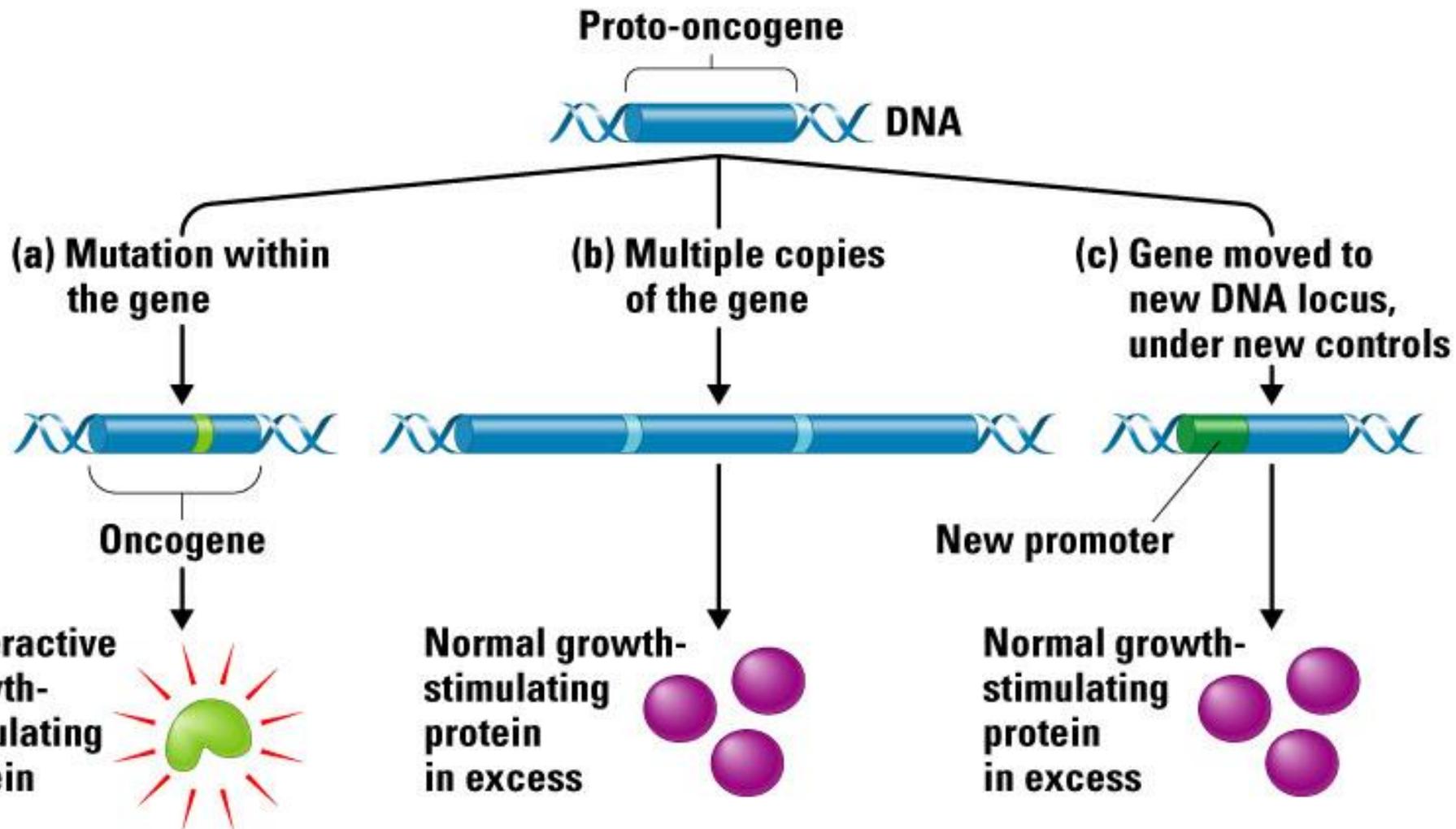
# Perda do controle do **Ciclo celular**



**Proto-oncogene vs. oncogene**

# Perda do controle do **Ciclo celular**

## Proto-oncogene vs. oncogene



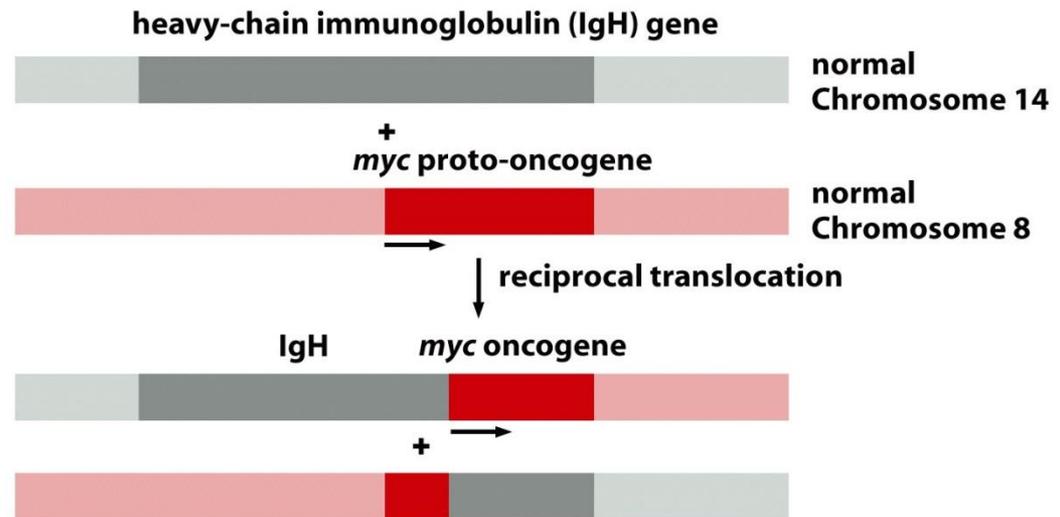
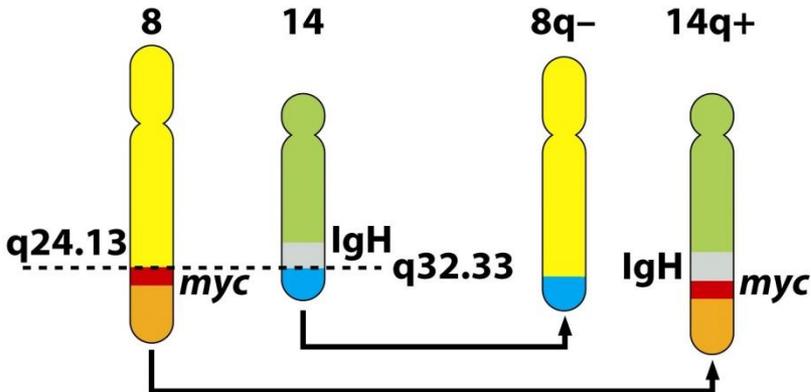
# Perda do controle do **Ciclo celular**

## Proto-oncogene vs. oncogene

### Linfoma de Burkitt

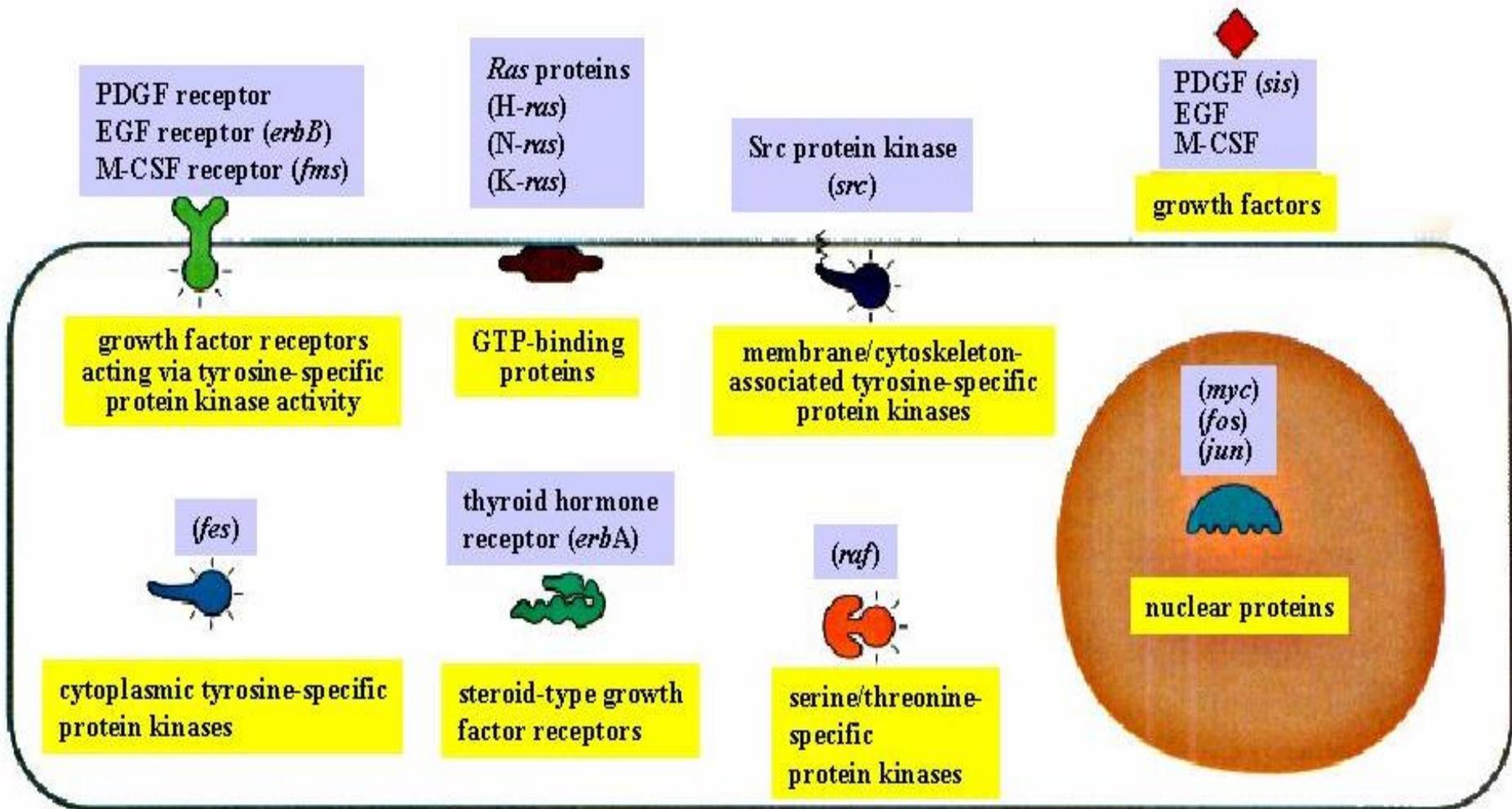
normal chromosomes

Burkitt's lymphoma  
t(8;14)



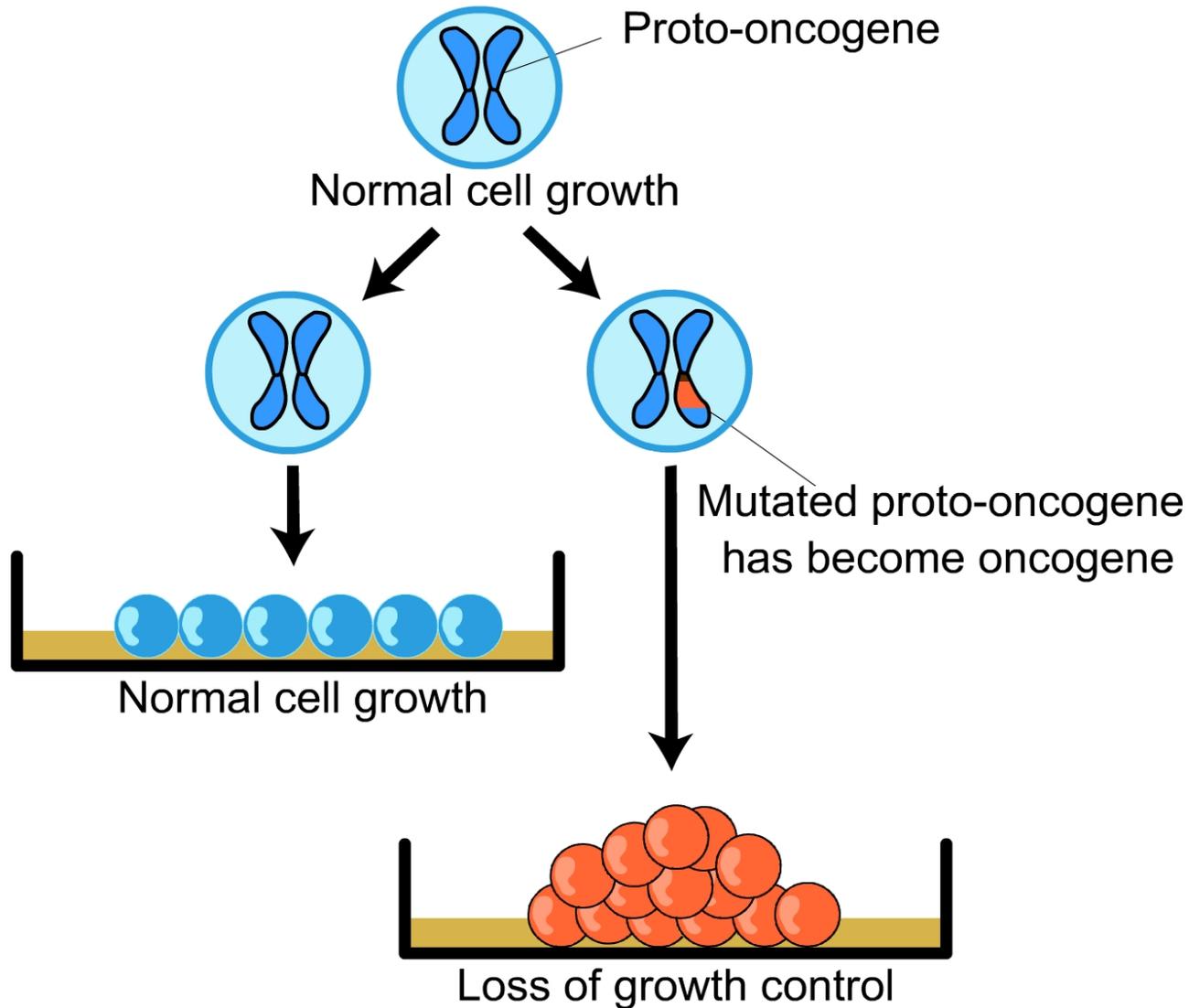
# Perda do controle do **Ciclo celular**

## Proto-oncogene vs. oncogene



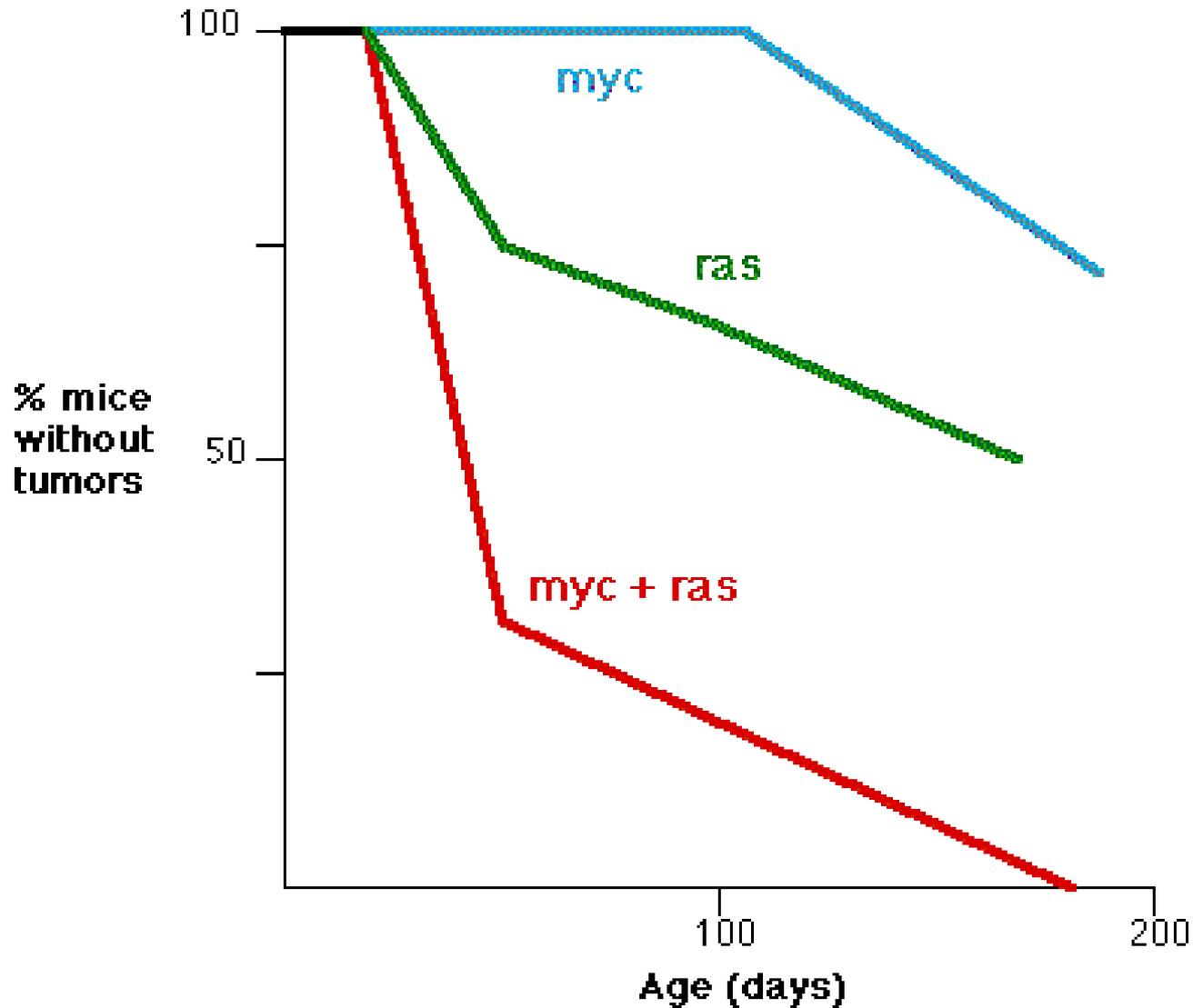
# Perda do controle do **Ciclo celular**

## Proto-oncogene vs. oncogene



# Perda do controle do **Ciclo celular**

## Colaboração entre oncogenes



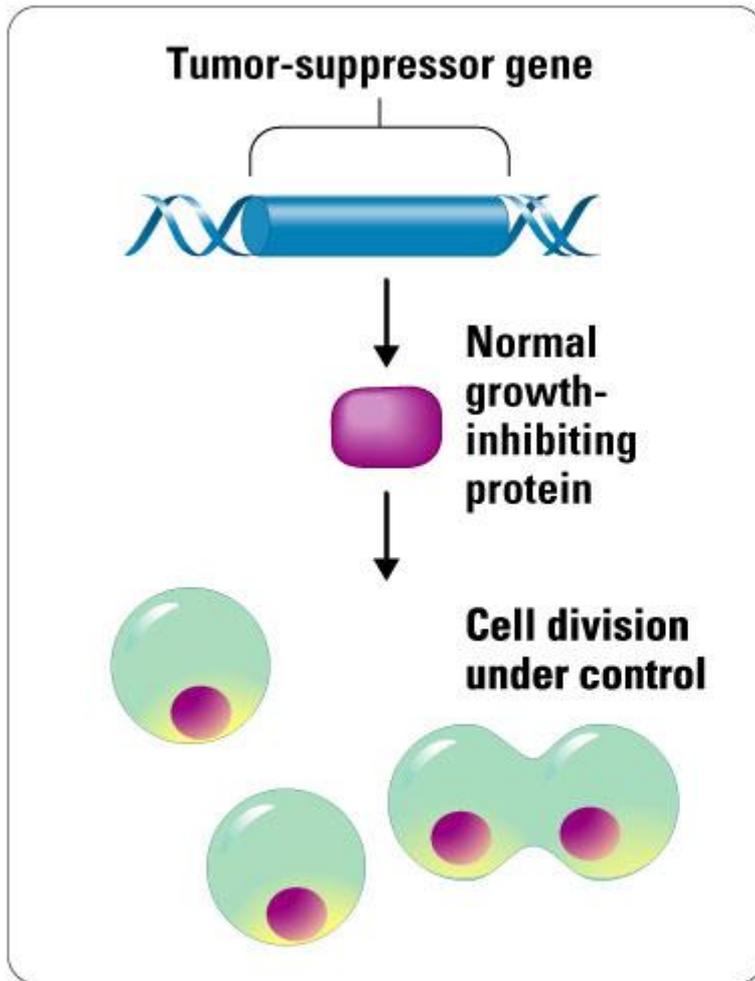
# Perda do controle do **Ciclo celular**

## Supressores de tumor e sua perda

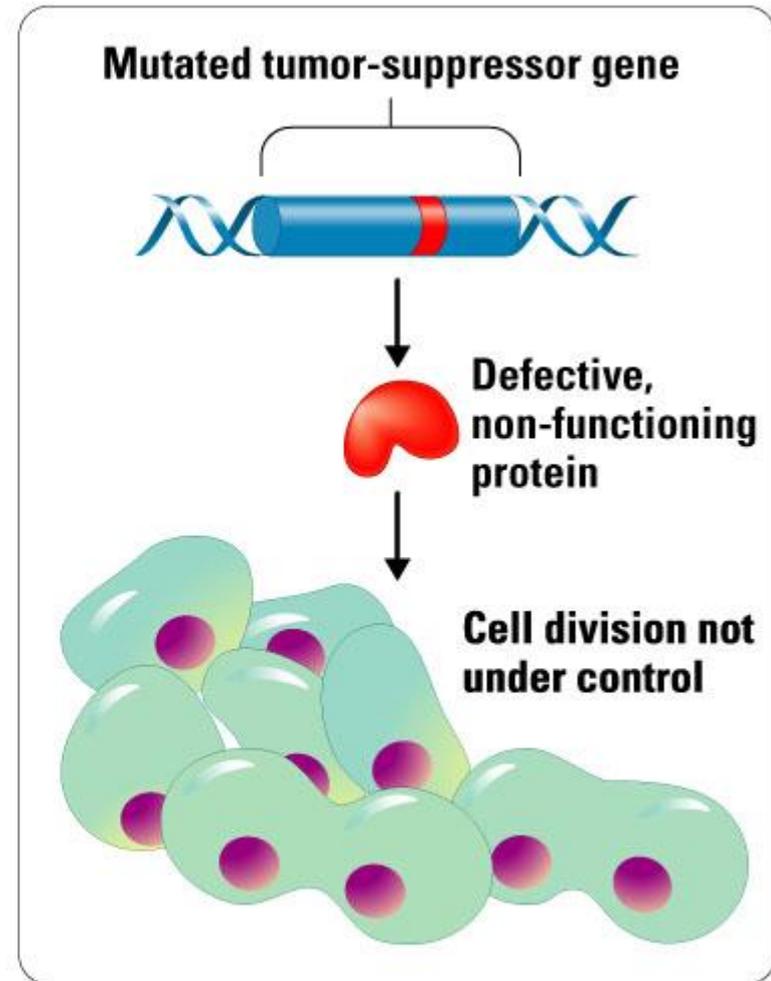
- Genes celulares que codificam fatores que inibem a proliferação celular
- As mutações nestes genes são recessivas

# Perda do controle do **Ciclo celular**

## Supressores de tumor e sua perda



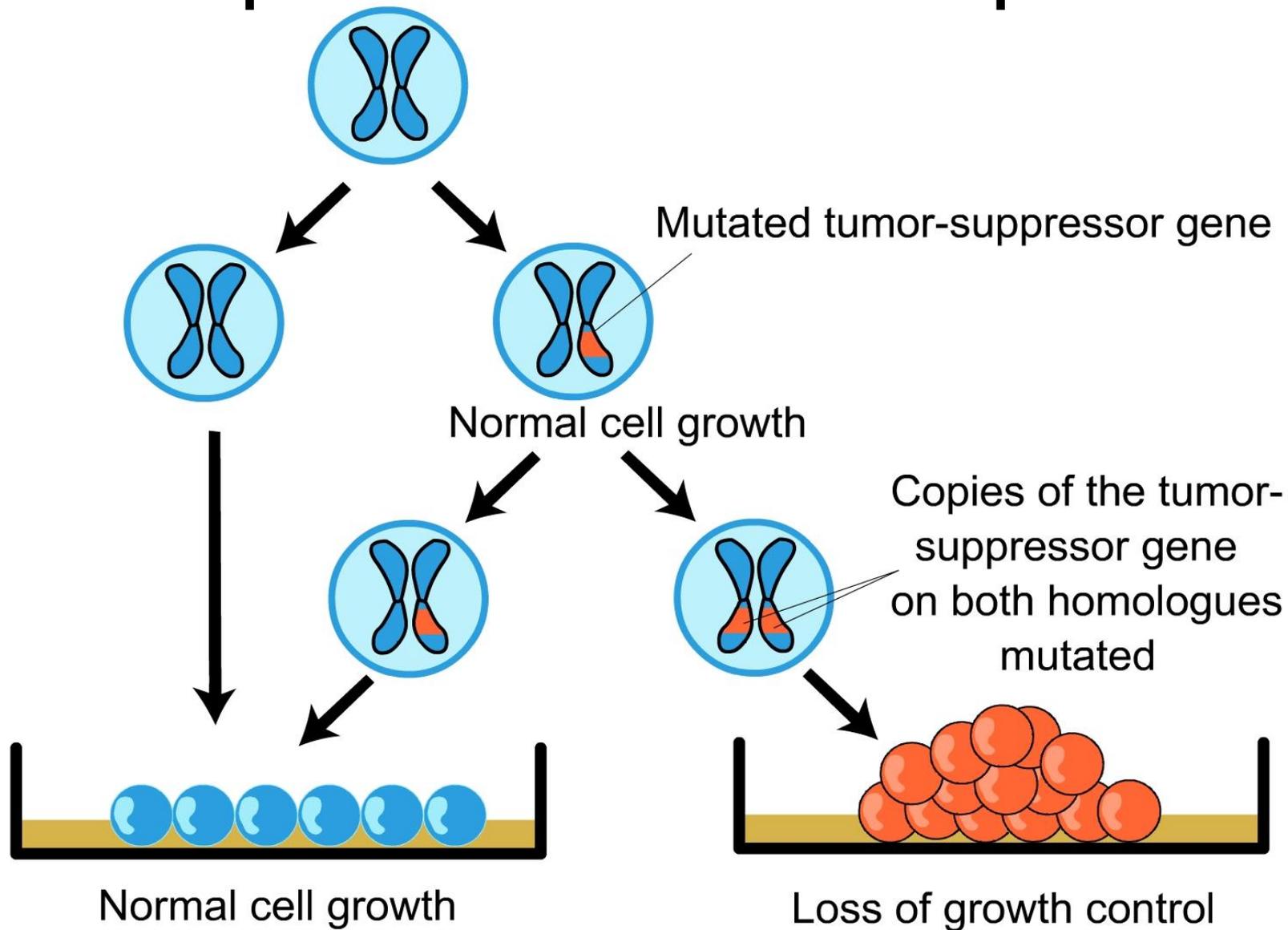
**(a)**



**(b)**

# Perda do controle do **Ciclo celular**

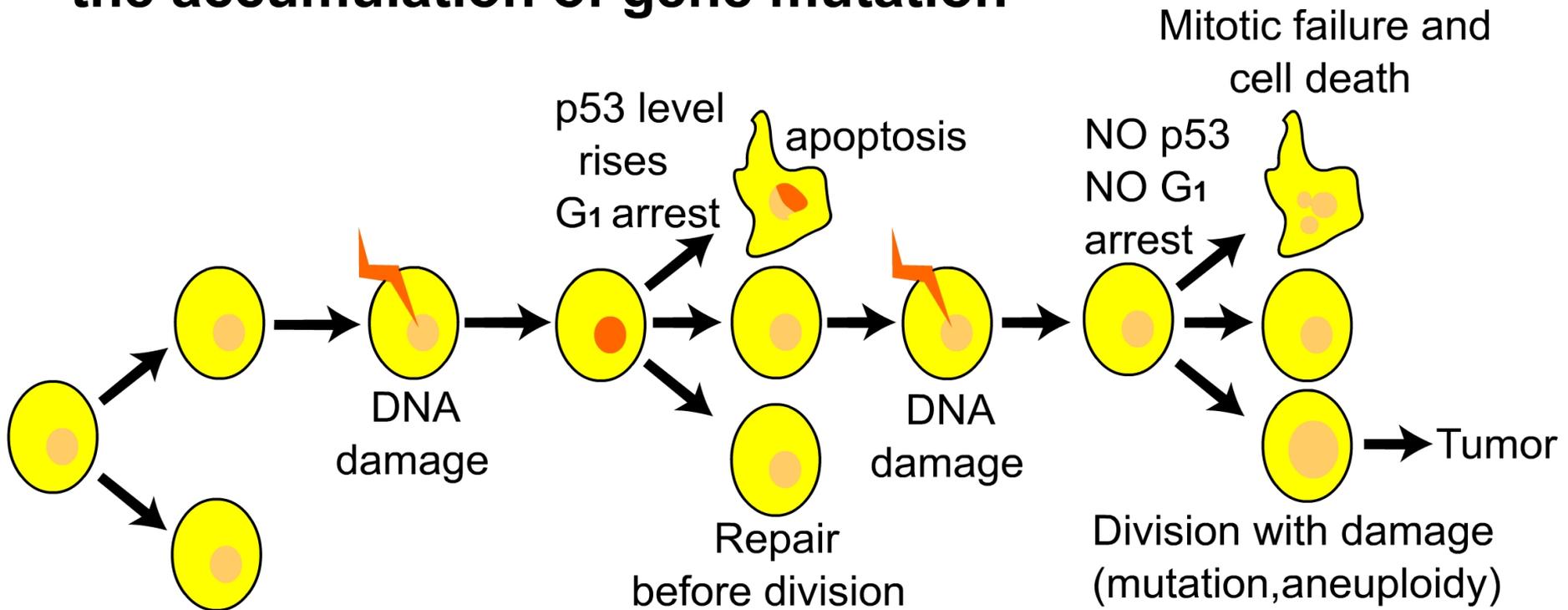
## Supressores de tumor e sua perda



# Perda do controle do **Ciclo celular**

## Supressores de tumor e sua perda

### the accumulation of gene mutation



# **Perda do controle do Ciclo celular**

**Supressores de tumor e sua perda**

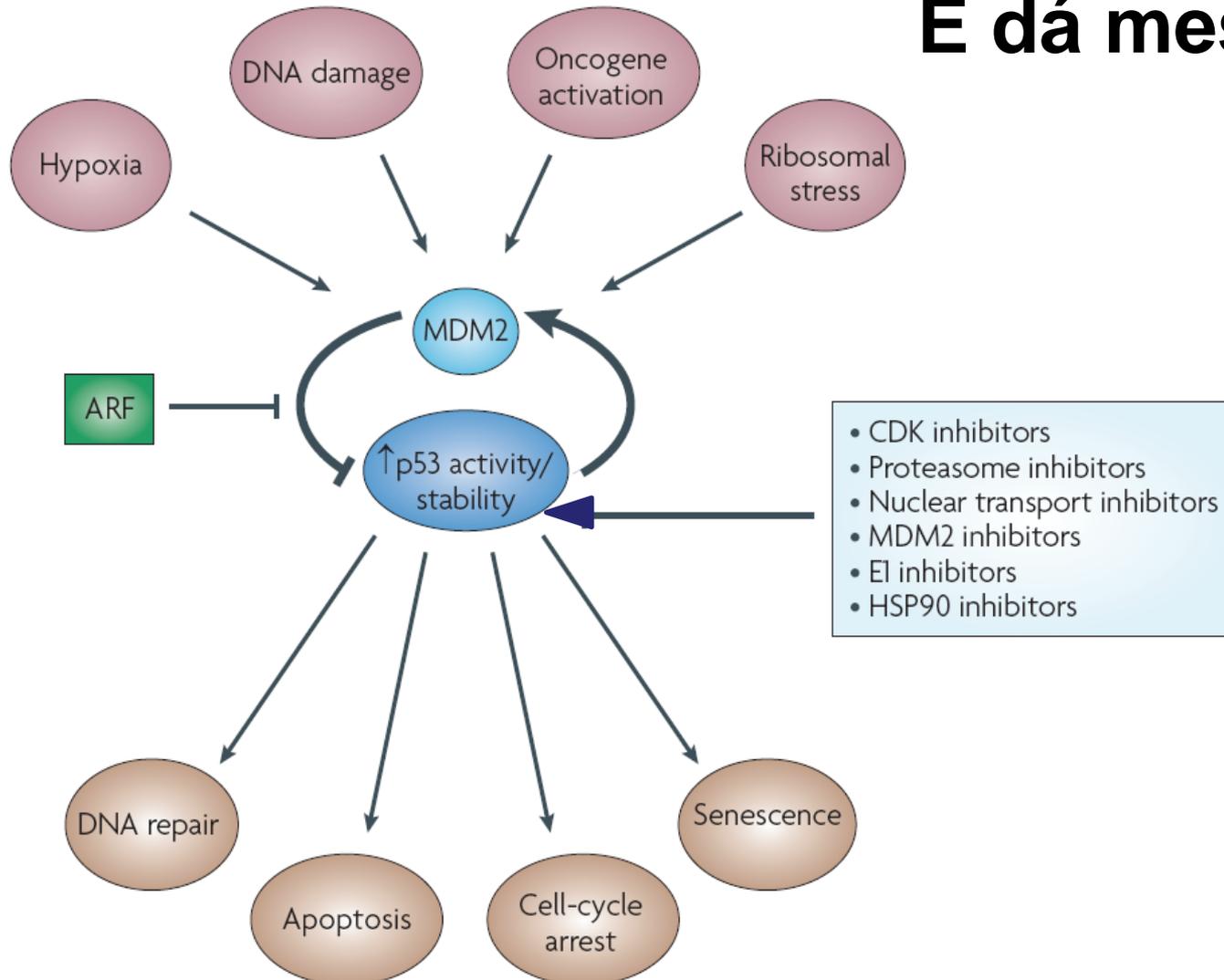
**p53 o “guardião do Genoma”**

**Isso deve dar trabalho...**

# Perda do controle do **Ciclo celular**

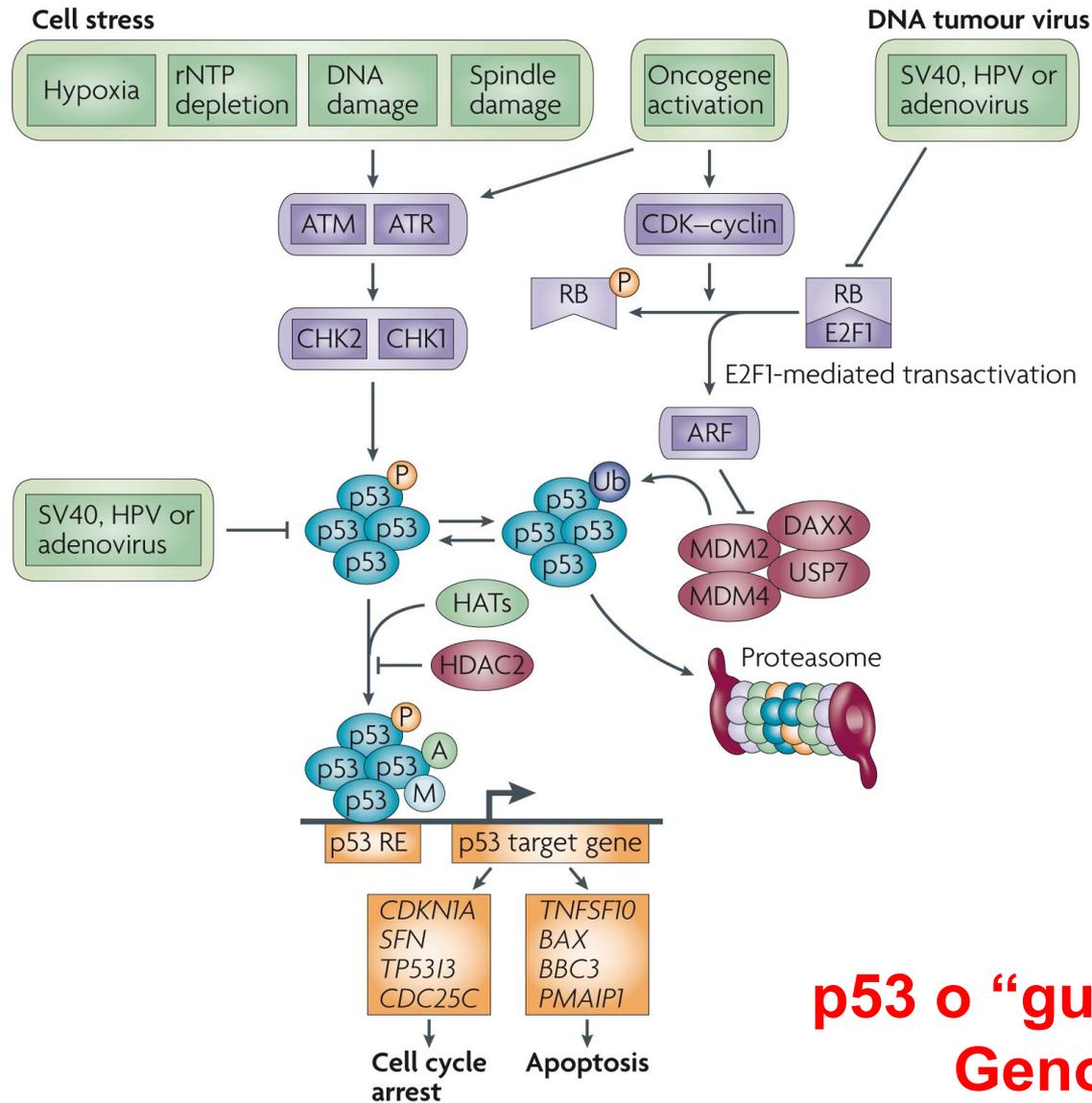
## Supressores de tumor e sua perda

**E dá mesmo!!!**



# Perda do controle do **Ciclo celular**

## Supressores de tumor e sua perda



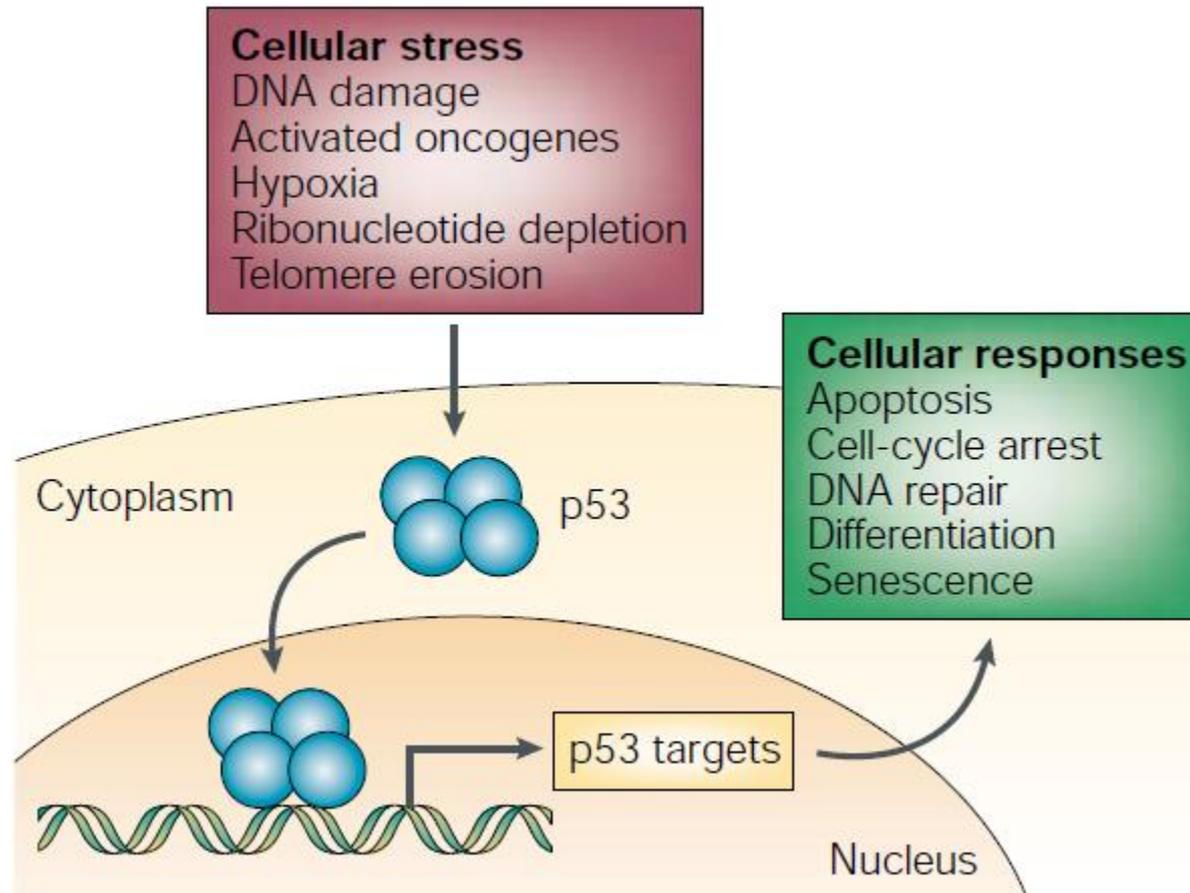
**p53 o “guardião do Genoma”**

# Perda do controle do **Ciclo celular**

## Supressores de tumor e sua perda

### p53 o “guardião do Genoma”

Ativar a via de p53 pode promover apoptose

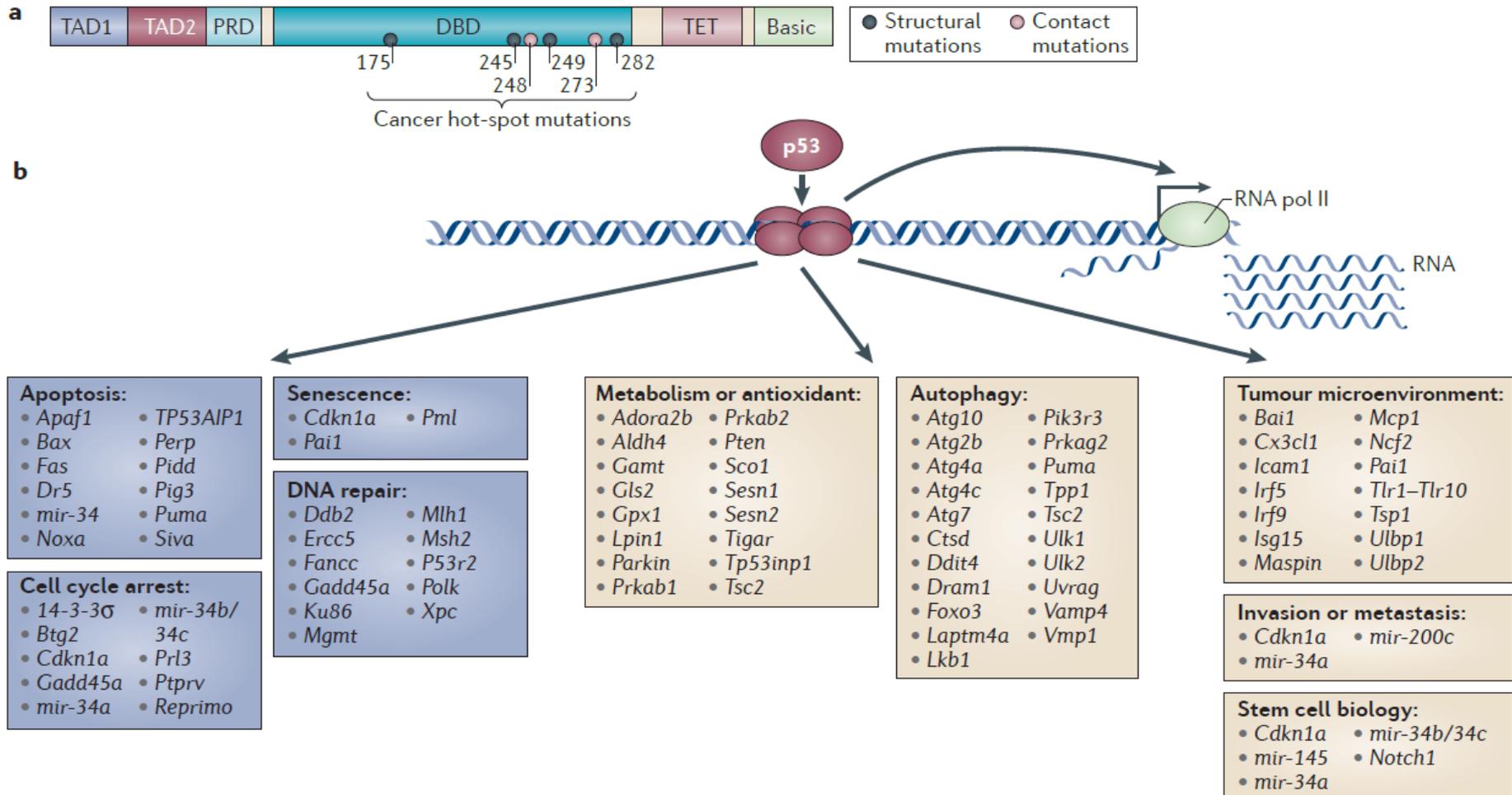


# Perda do controle do **Ciclo celular**

## Supressores de tumor e sua perda

### p53 o “guardião do Genoma”

Ativar a via de p53 pode promover várias respostas.

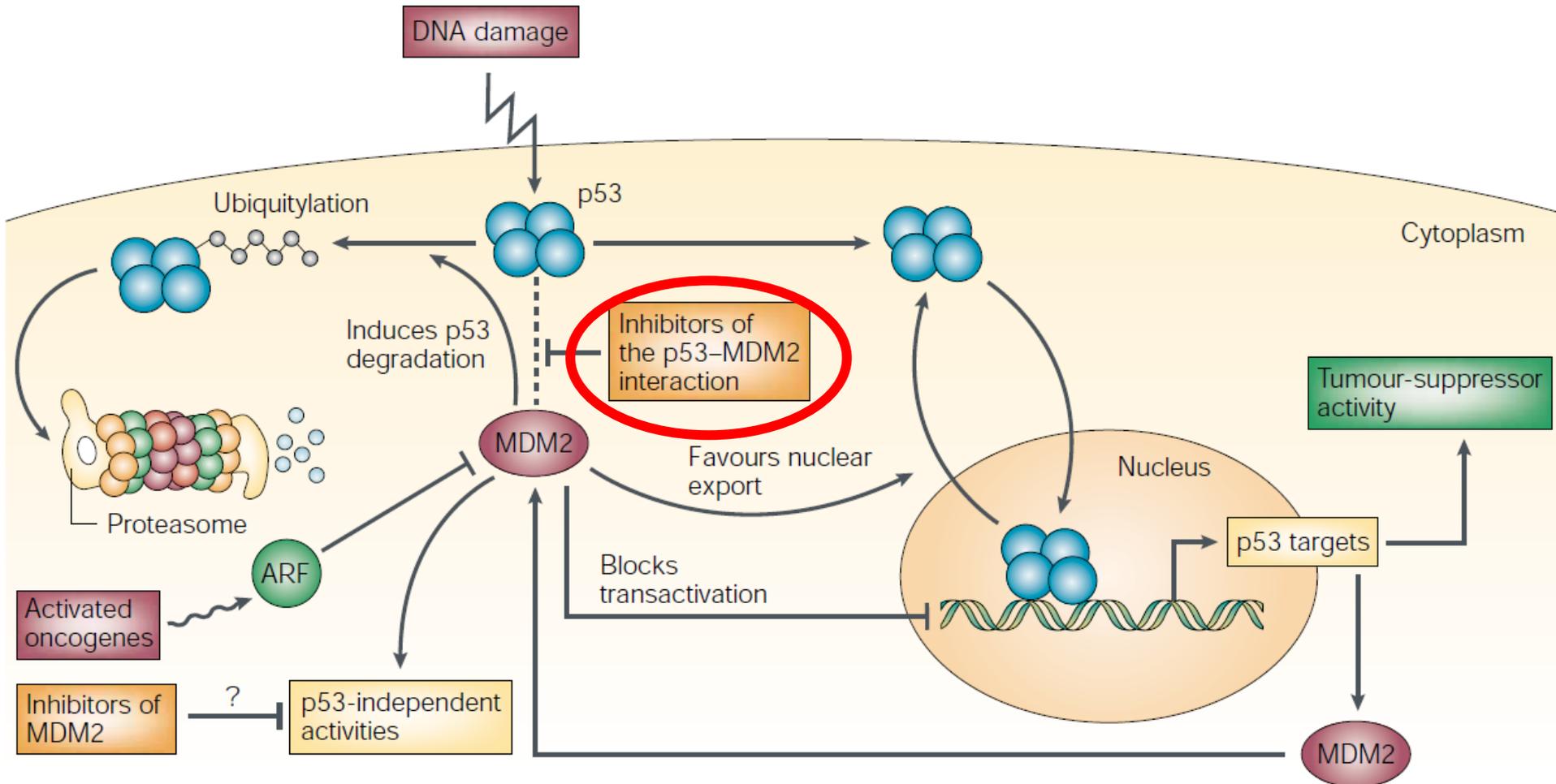


# Perda do controle do **Ciclo celular**

## Supressores de tumor e sua perda

### p53 o “guardião do Genoma”

- Via está muito bem regulada...e seus inibidores alterados em alguns tumores.



# Perda do controle do **Ciclo celular**

## Supressores de tumor e sua perda

### Inibidores da interação p53-MDM2

Table 1 | **Inhibitors of the p53-MDM2 interaction**

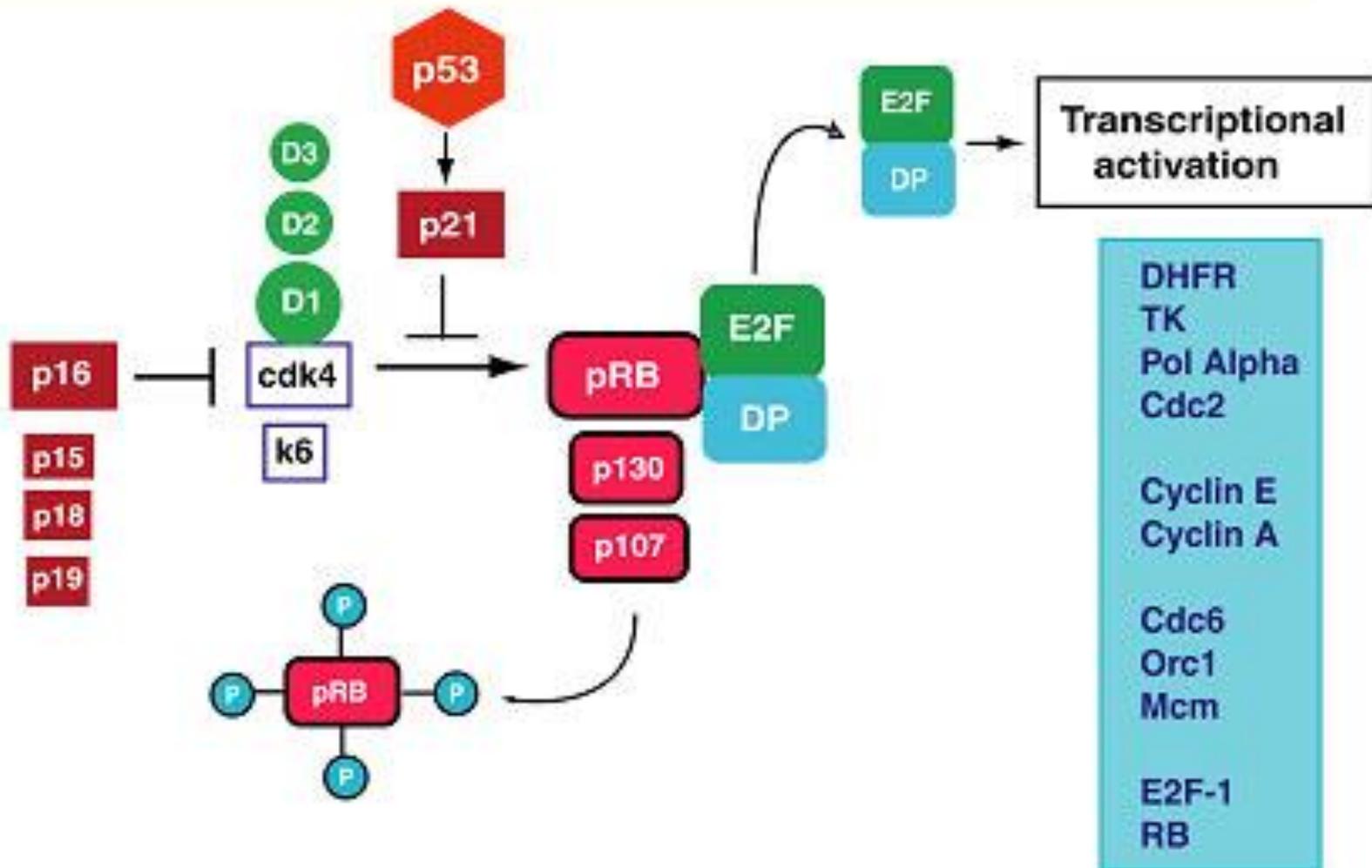
Compound	Structure	IC <sub>50</sub> (μM)	Type of compound	References
1	Ac-Gln-Glu-Thr-Phe <sup>19</sup> -Ser-Asp-Leu-Trp <sup>23</sup> -Lys-Leu-Leu <sup>26</sup> -Pro-NH <sub>2</sub>	8.7	Wild-type p53	
2	Ac-Met-Pro-Arg-Phe <sup>19</sup> -Met-Asp-Tyr-Trp <sup>23</sup> -Glu-Gly-Leu <sup>26</sup> -Asn-NH <sub>2</sub>	0.3	Phage-derived peptide	62
3	Ac-Phe <sup>19</sup> -Met-Asp-Tyr-Trp <sup>23</sup> -Glu-Gly-Leu <sup>26</sup> -Asn-NH <sub>2</sub>	8.9	Truncated phage-derived peptide	62
4	Ac-Glu-Thr-Phe <sup>19</sup> -Aib-Asp-Aib-Trp <sup>23</sup> -Lys-Aib-Leu <sup>26</sup> -Aib-Glu-NH <sub>2</sub>	5.2	Constrained wild-type peptide	61
5	Ac-Phe <sup>19</sup> -Met-Aib-Tyr-Trp <sup>23</sup> -Glu-Ac <sub>3</sub> c-Leu <sup>26</sup> -Asn-NH <sub>2</sub>	2.2	Constrained peptide 3	62
6	Ac-Phe <sup>19</sup> -Met-Aib-Pmp-Trp <sup>23</sup> -Glu-Ac <sub>3</sub> c-Leu <sup>26</sup> -Asn-NH <sub>2</sub>	0.3	Peptide 5 with a PMP at position 22	62
7	Ac-Phe <sup>19</sup> -Met-Aib-Pmp-6ClTrp <sup>23</sup> -Glu-Ac <sub>3</sub> c-Leu <sup>26</sup> -Asn-NH <sub>2</sub>	0.005	Peptide 6 with a 6ClTrp at position 22	62

# Perda do controle do **Ciclo celular**

## Supressores de tumor e sua perda

Via de pRb/E2F

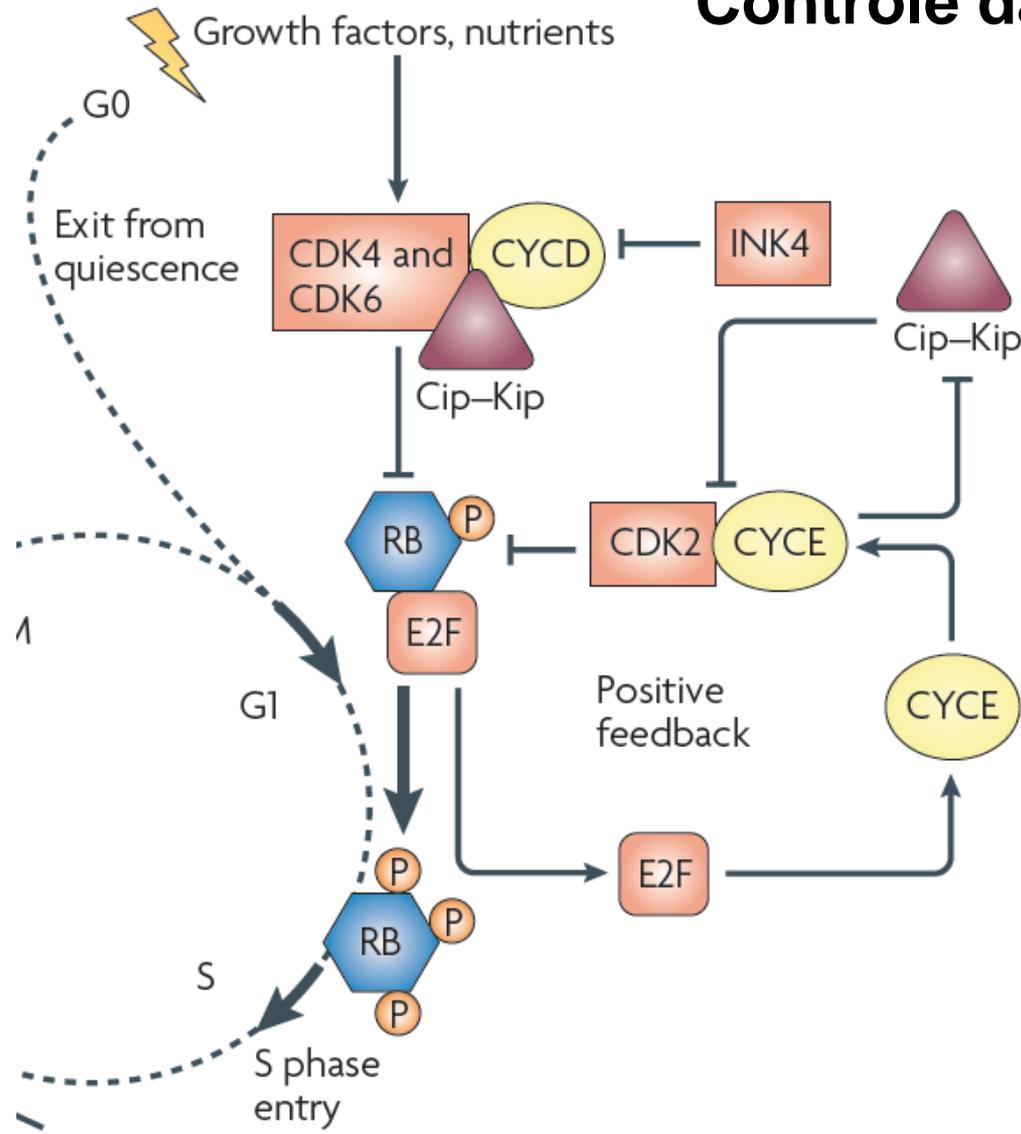
Controle da transição G1/S



# Perda do controle do **Ciclo celular**

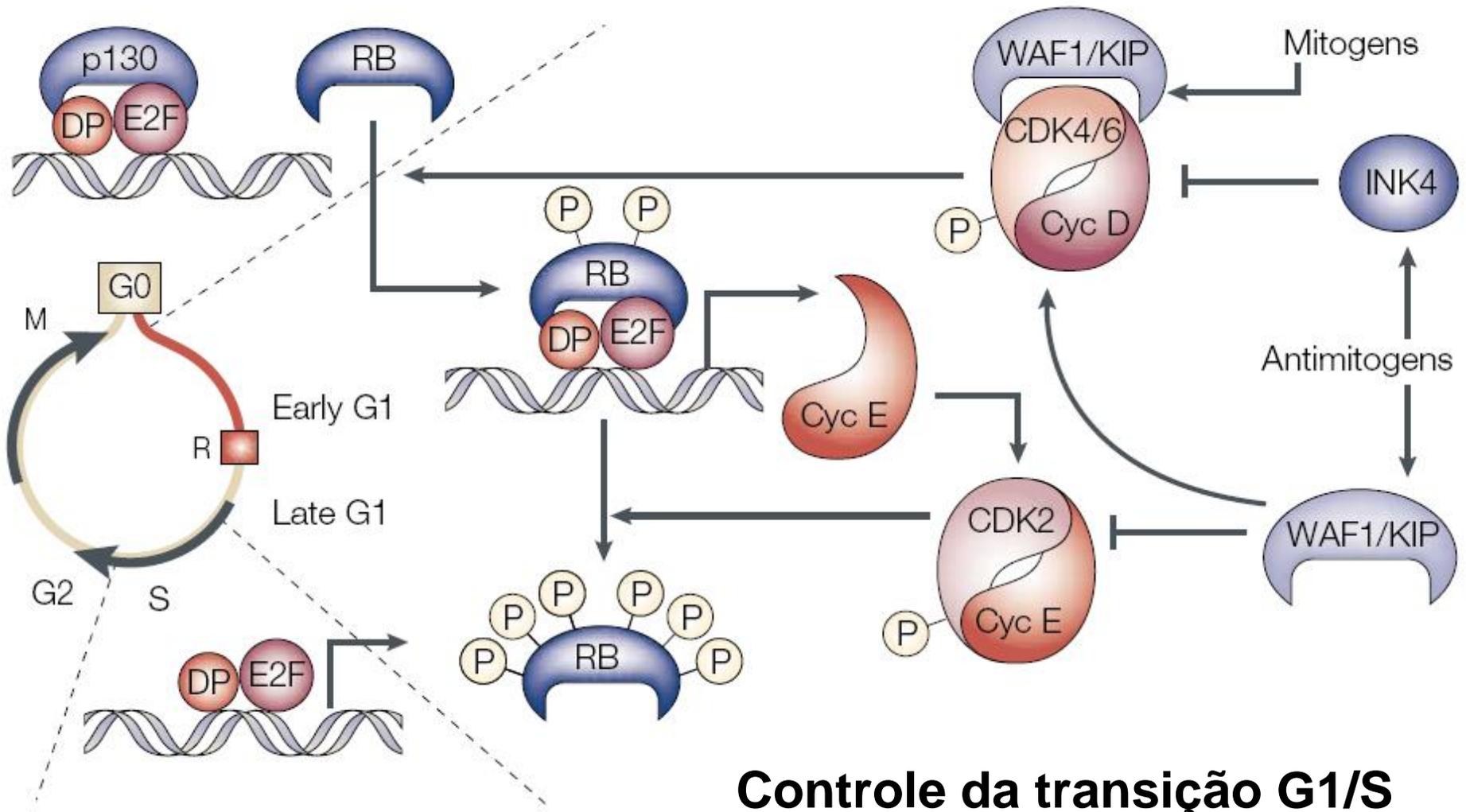
## Supressores de tumor e sua perda

### Controle da transição G1/S



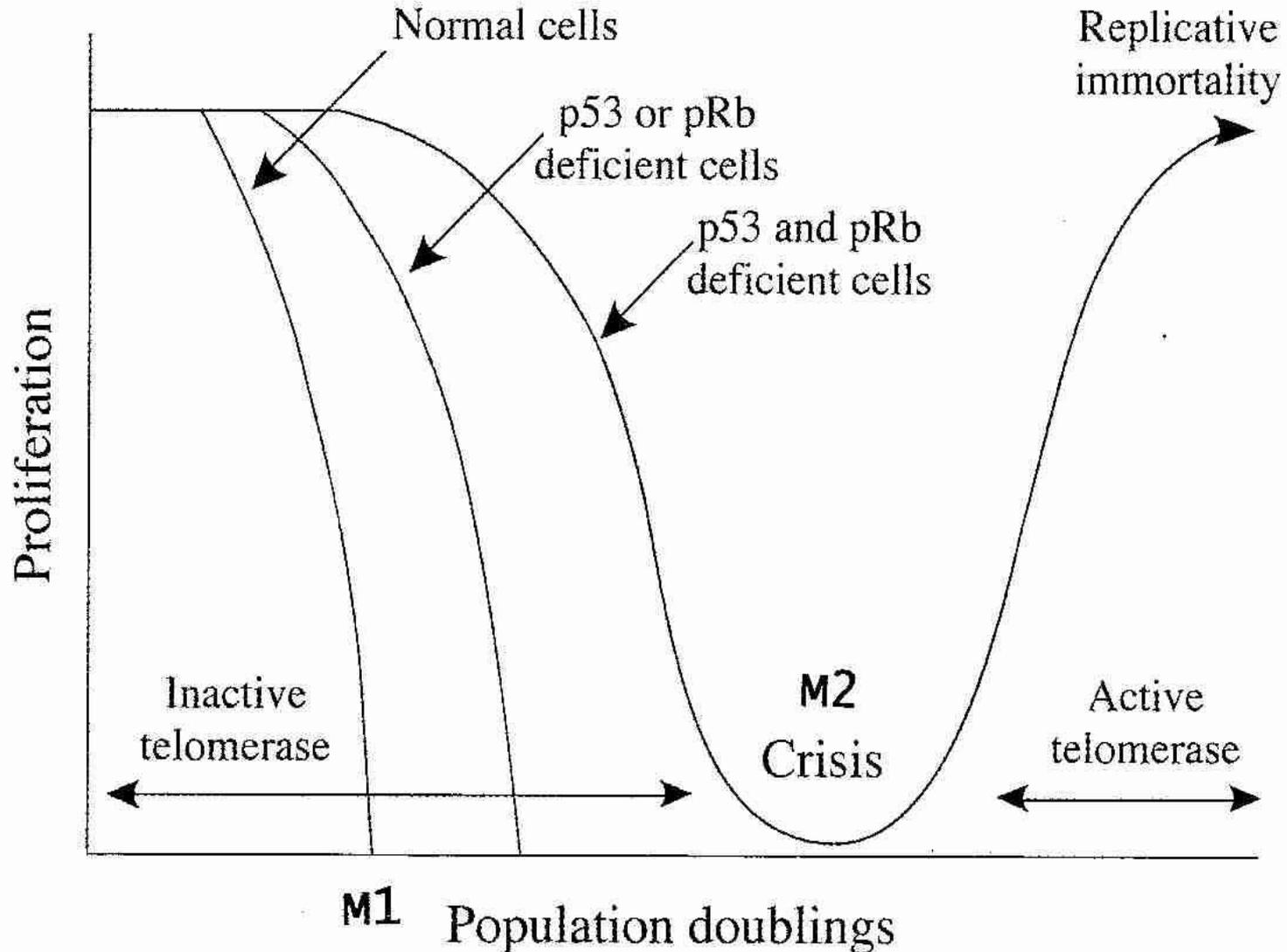
# Perda do controle do **Ciclo celular**

## Supressores de tumor e sua perda



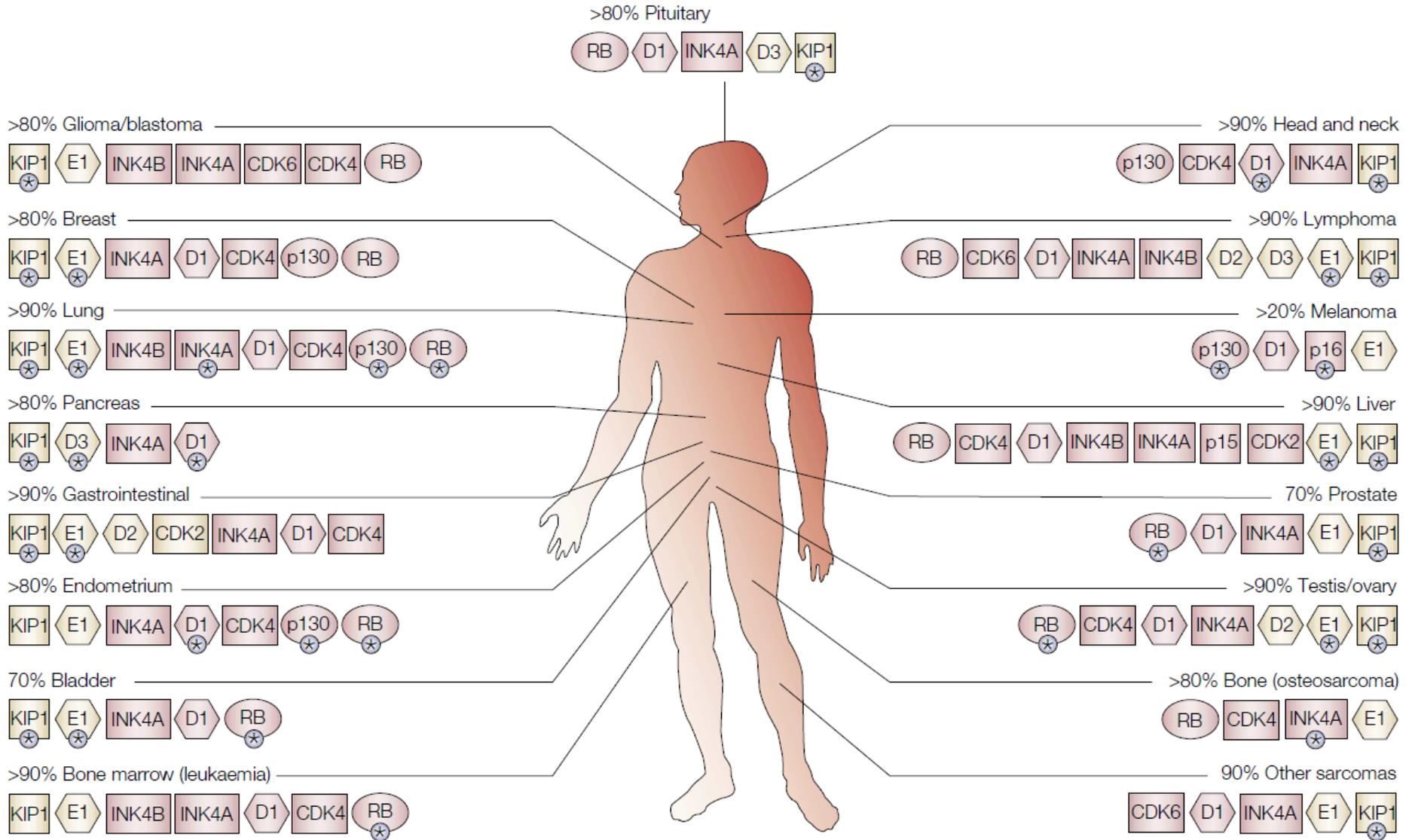
# Perda do controle do **Ciclo celular**

## Supressores de tumor e sua perda



# Perda do controle do Ciclo celular

## Alterações na transição G1/S



# Controle da transição G1/S: inibidores de CKDs

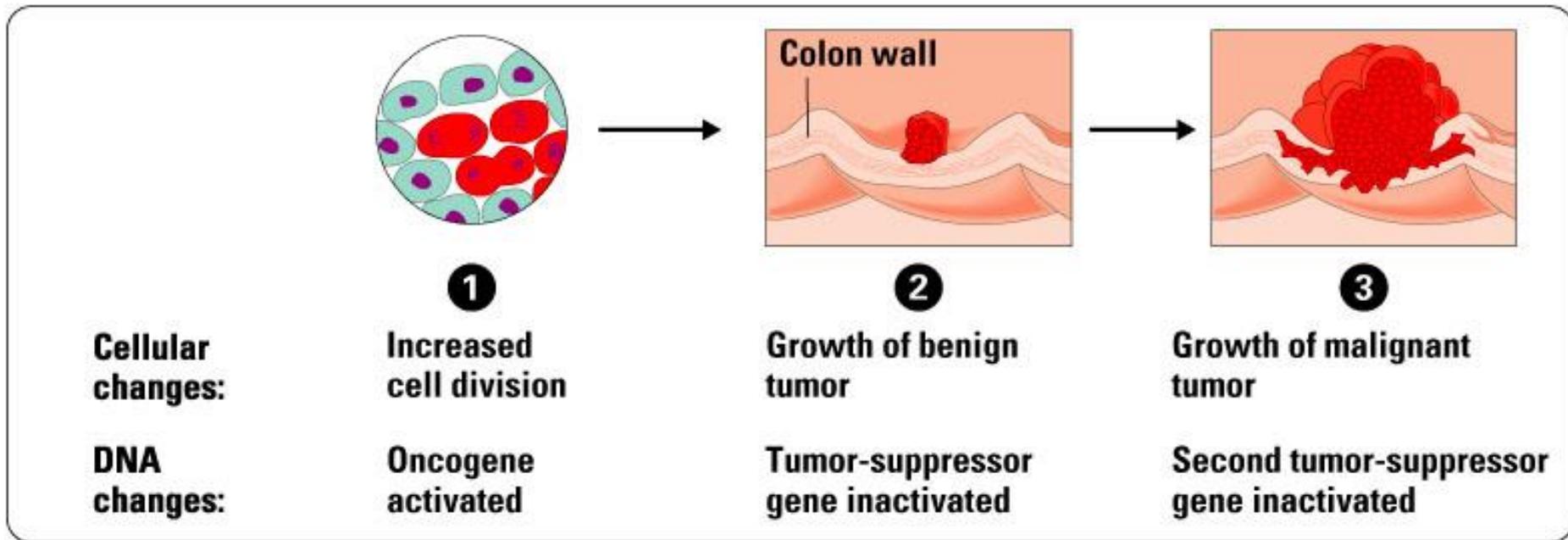
Table 1 | **Small-molecule CDK inhibitors**

Compound	Family	Specificity	Features	References
Olomoucine	Purines	CDK1, CDK2 and CDK5 >> CDK4	Growth arrest in G1/S and G2/M. Induces apoptosis.	110
Roscovitine	Purines	CDK1, CDK2 and CDK5 >> CDK4	Growth arrest in G1/S and G2/M. Induces apoptosis and differentiation in some cases.	110
Purvalanol	Purines	CDK1, CDK2, CDK5	Growth arrest in G1/S and G2/M.	75
NU2058 and NU6027	Purine/ pyrimidine	CDK1, CDK2	Growth inhibition of tumour cells.	111
UCN-01*	Alkaloids	CDK1, CDK2, CDK4	Growth inhibition and apoptosis. Induces G1/S and G2/M arrest. Some activity in clinical trials against melanoma, lymphoma and sarcoma.	80
Indirubin-5-sulphonic acid	Indirubins	CDK1 > CDK5 > CDK2 >> CDK4	The founder of this class, indirubin, is the active component of a traditional Chinese recipe against leukaemia.	79
Flavopiridol*	Flavonoid	CDK1, CDK2, CDK4	Growth arrest in G1/S and G2/M. Also induces apoptosis and differentiation. Clinical trials have shown some activity against lymphoma, and colon and renal cancer.	80
Kenpaullone	Paullones	CDK1 > CDK2 >> CDK4	Delayed cell-cycle progression. Inhibits growth of tumour cells <i>in vitro</i> .	112
Butyrolactone I	Natural product	CDK1 > CDK2	Isolated from <i>Aspergillus</i> . Growth arrest in G1/S and G2/M. Also induces apoptosis and differentiation in some systems.	113
Hymenialdisine	Natural product	CDK1, CDK5 > CDK2 >> CDK4	Isolated from a marine sponge.	114
SU9516	Indolinone	CDK2	Decrease in RB phosphorylation and caspase-3 activation. Causes G0/G1 and G2/M block.	115
CINK4	Triamino-pyrimidine	CDK4/6–cyclin D1	Causes RB dephosphorylation and growth arrest in culture and smaller tumours in a xenograft model.	116
PD 0183812	Pyrido-pyrimidine	CDK4, CDK6 > CDK2	G1 arrest in RB-positive cells, in correlation with RB hypophosphorylation.	117
Fascaplysin	Natural product	CDK4	G1 arrest and RB dephosphorylation at sites that are specific for CDK4 kinase.	118

Asterisks refer to compounds tested in clinical trials. CDK, cyclin-dependent kinase; RB, retinoblastoma.

# Perda do controle do **Ciclo celular**

## **Resumindo:** Supressores de tumor vs. oncogenes

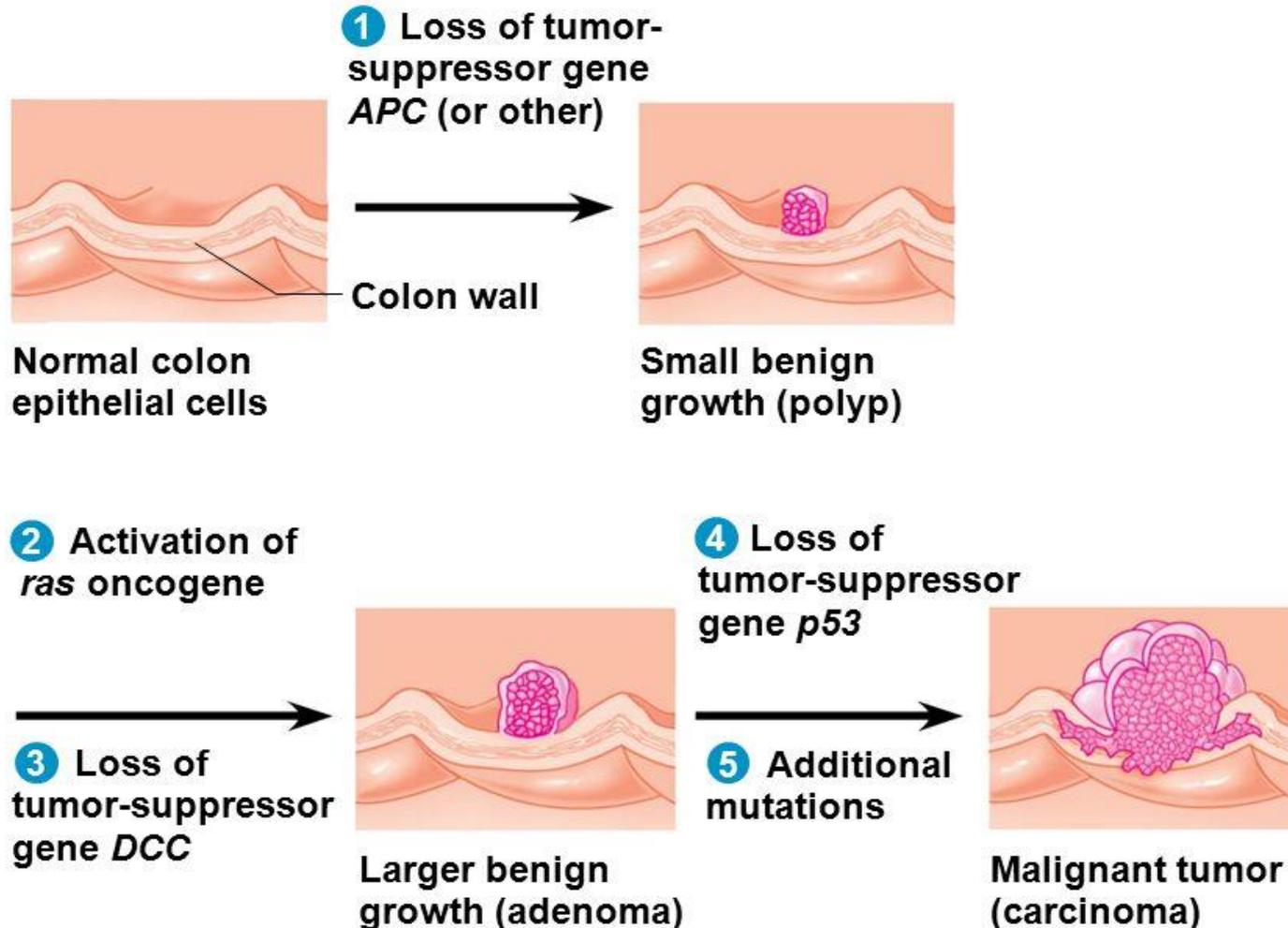


**(a) Stepwise development of a typical colon cancer**

# Perda do controle do **Ciclo celular**

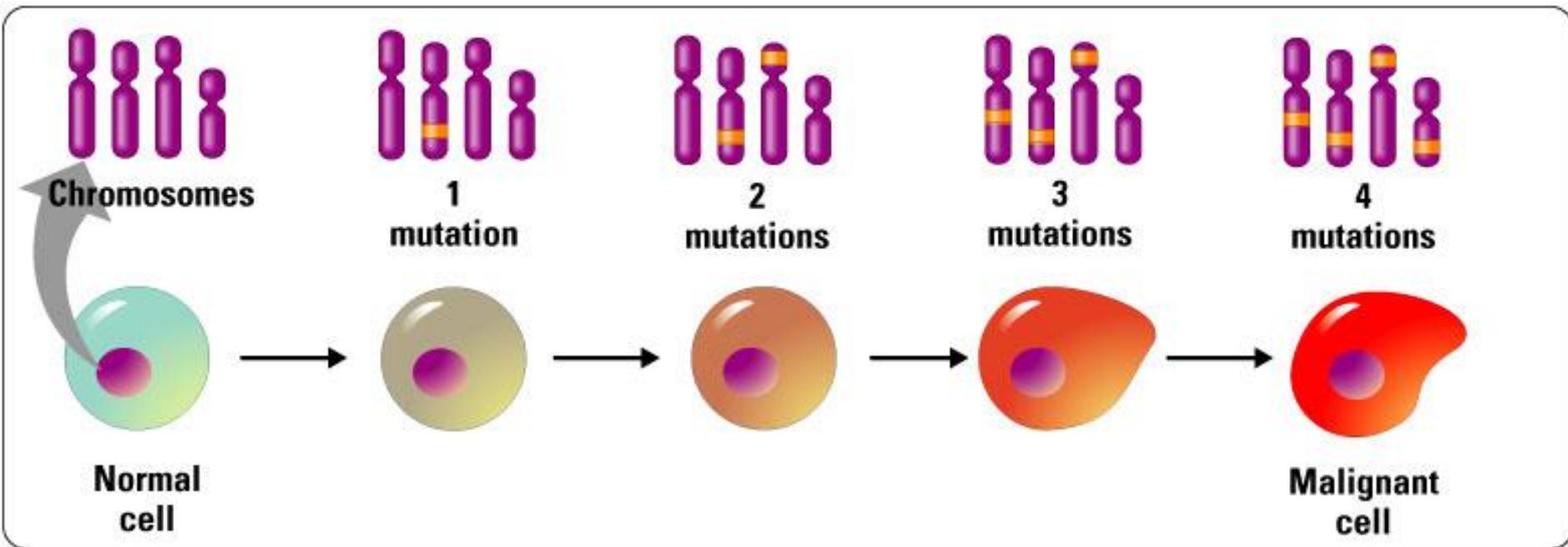
## Resumindo: Supressores de tumor vs. oncogenes

Figure 16.19a



# Perda do controle do **Ciclo celular**

**Resumindo:** Supressores de tumor vs. oncogenes

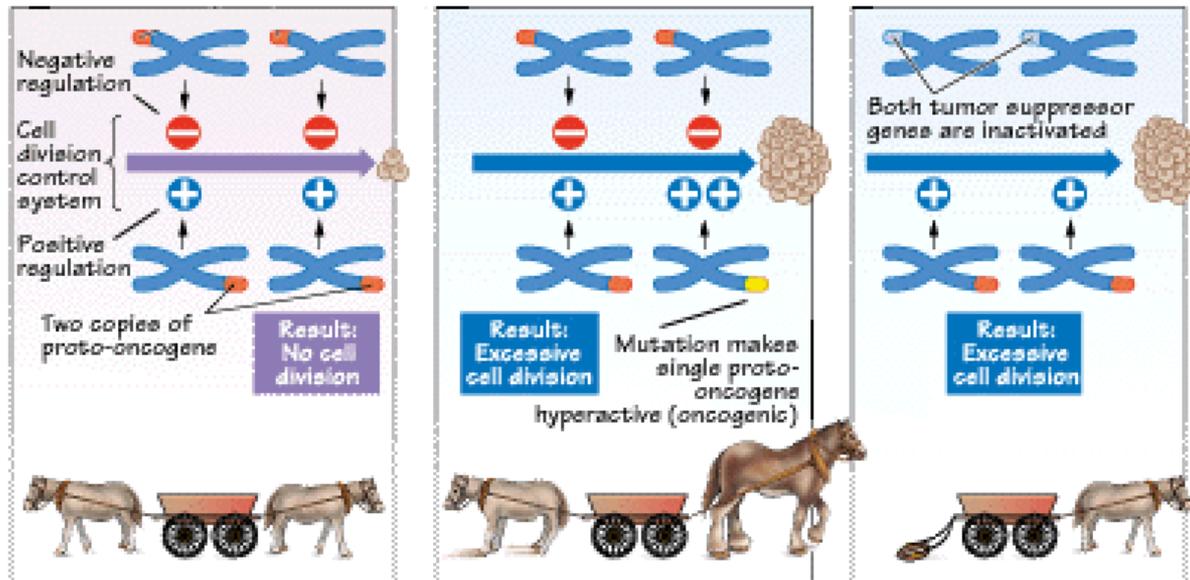


**(b) Accumulation of mutations in the development of a cancer cell**

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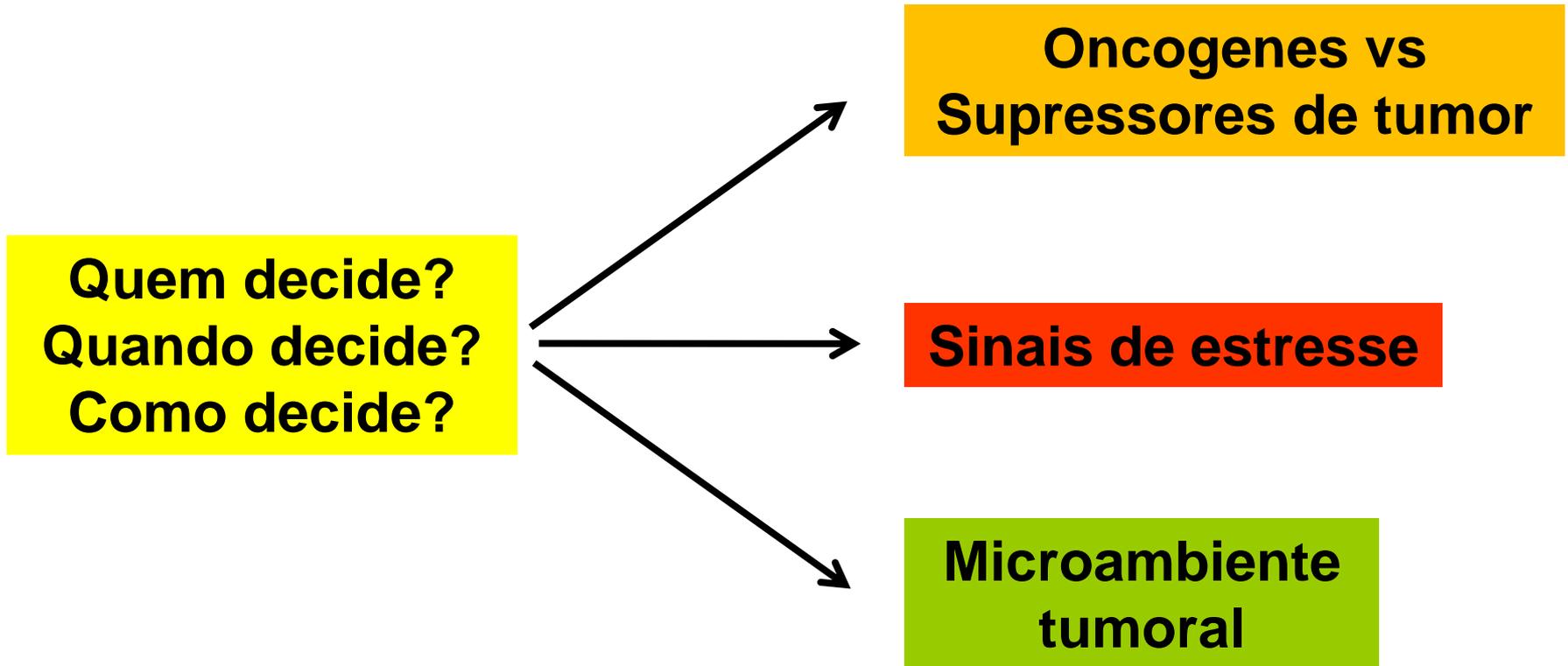
# Perda do controle do **Ciclo celular**

**Resumindo:** Supressores de tumor vs. oncogenes



# Controle do Ciclo celular

## Morte vs Proliferação



# Controle do Ciclo celular

## Morte vs Proliferação

### Tumour acquired capabilities

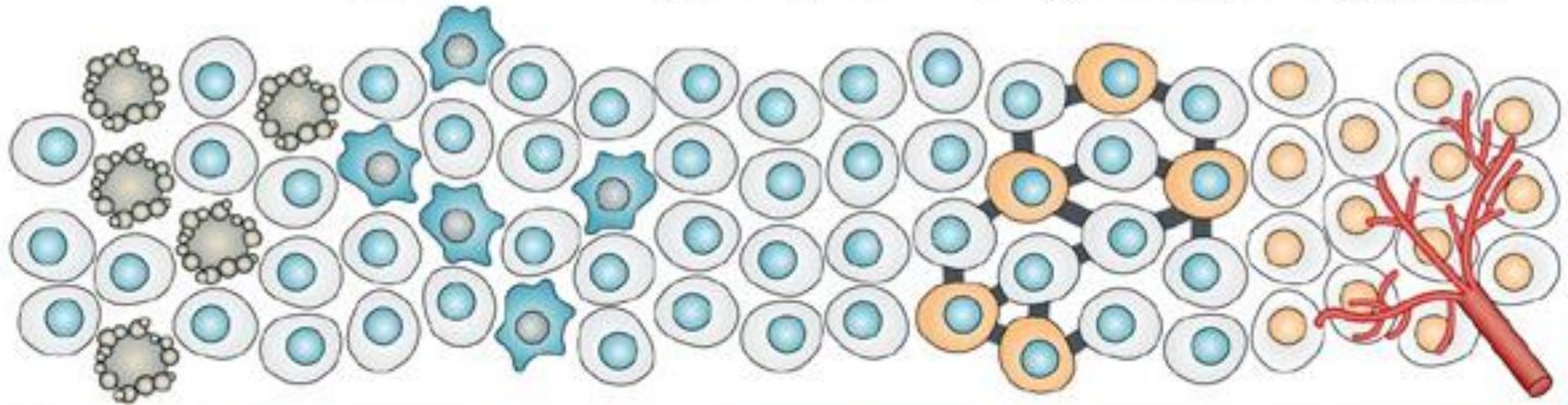
Evading apoptosis

Limitless replicative potential

Self-sufficiency in growth signals

Insensitivity to anti-growth signals

Sustained angiogenesis

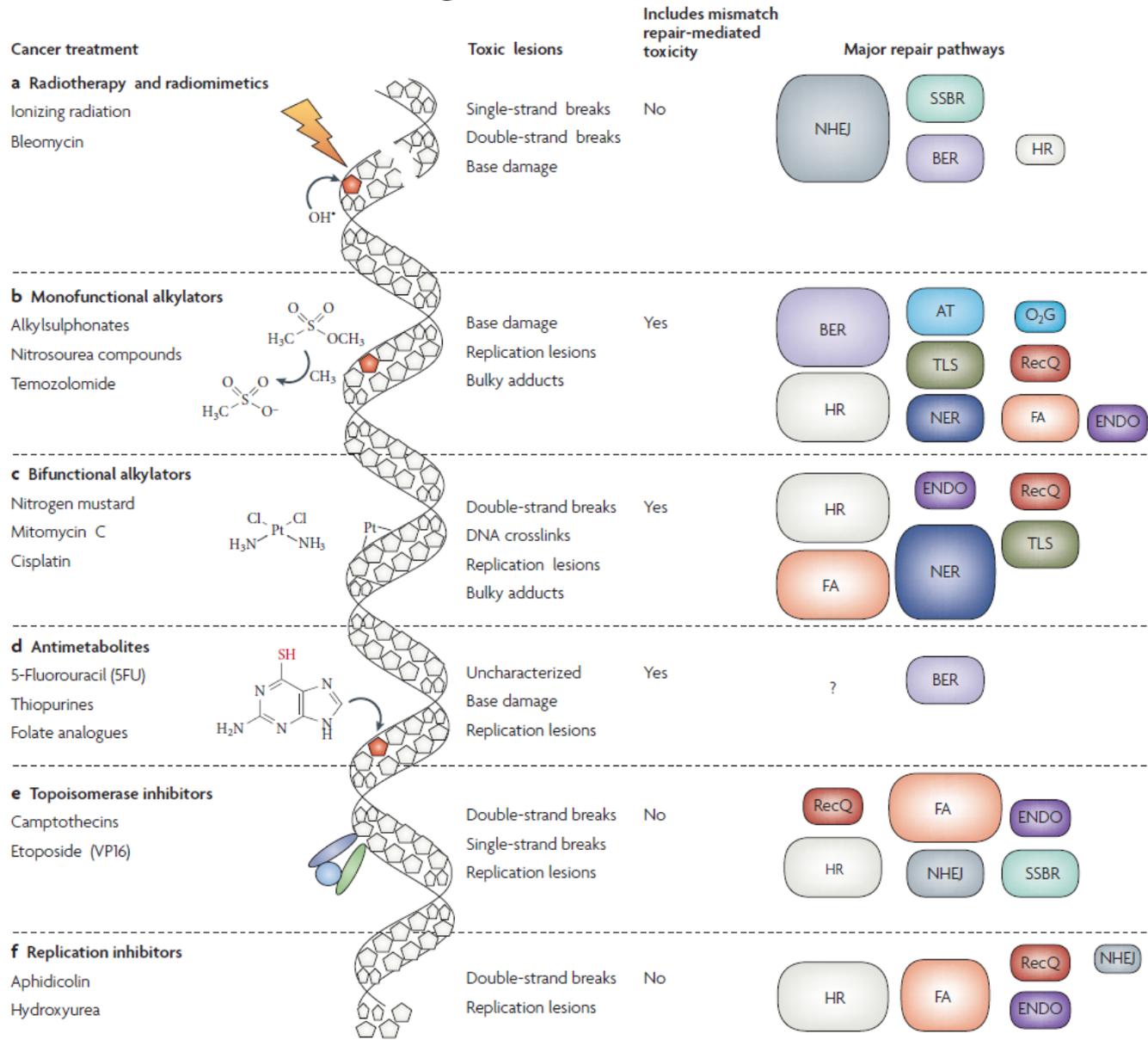


Environmental capacity

Cell-autonomous capabilities

# Controle do Ciclo celular

## Morte vs. Proliferação: deslocando o equilíbrio



**Obrigado!!!**