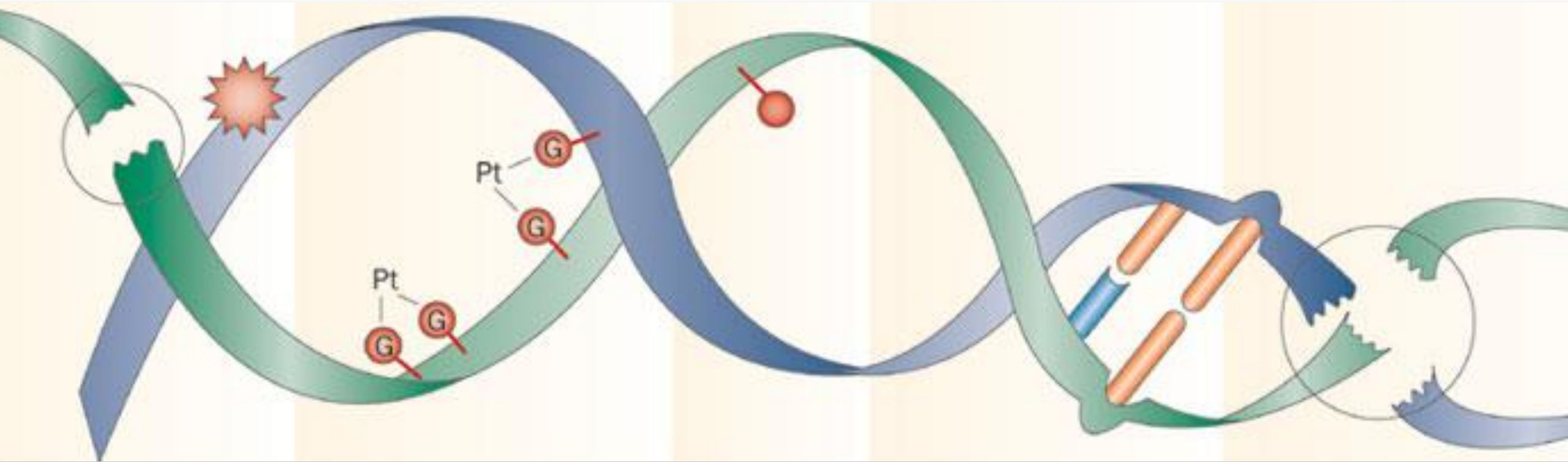
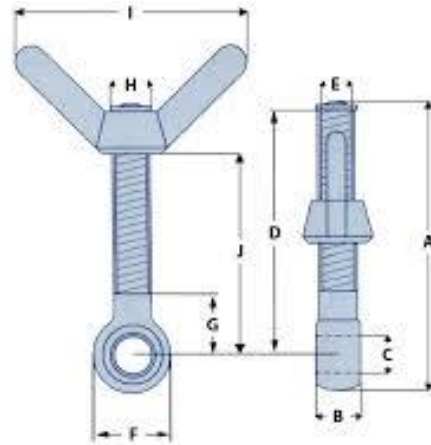
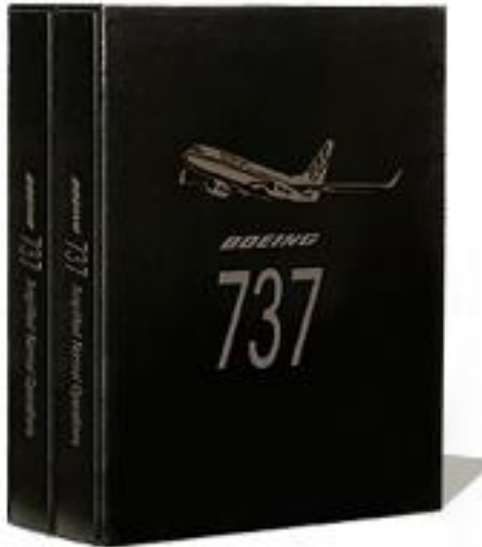
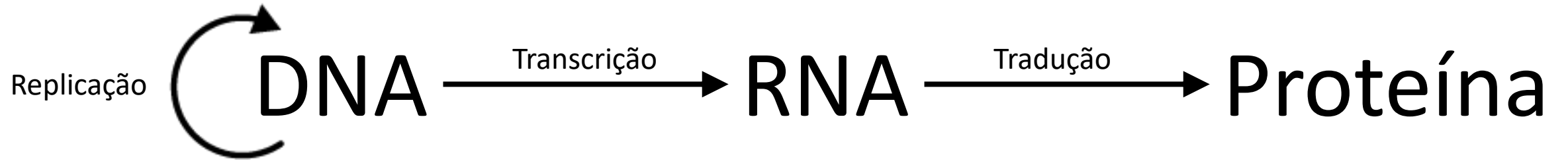


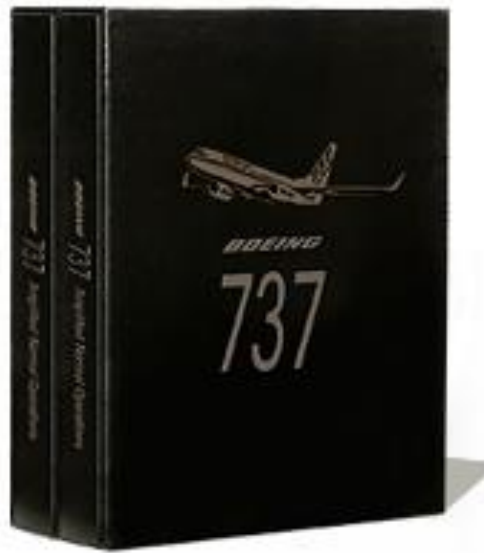
# Reparo do DNA



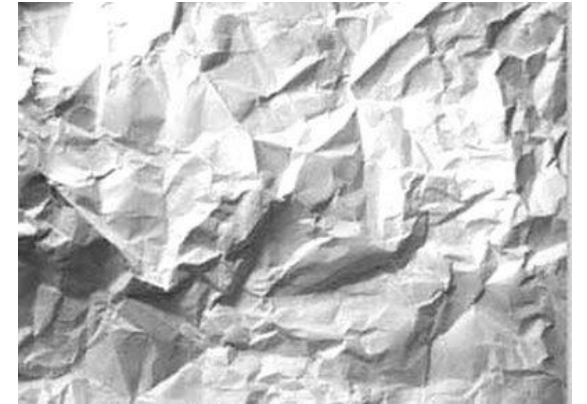
# Dogma (original)



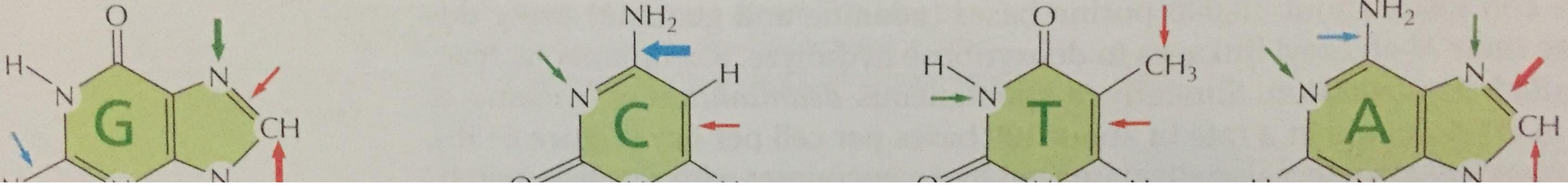
# Manutenção do Manual = Reparo de DNA



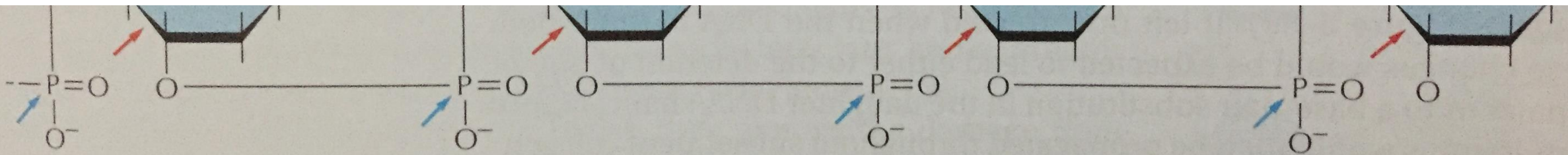
Tempo/uso



# Tamanho do problema



1.000.000.000.000.000



$10^4$ -  $10^5$  por célula por dia

+ erros durante a replicação

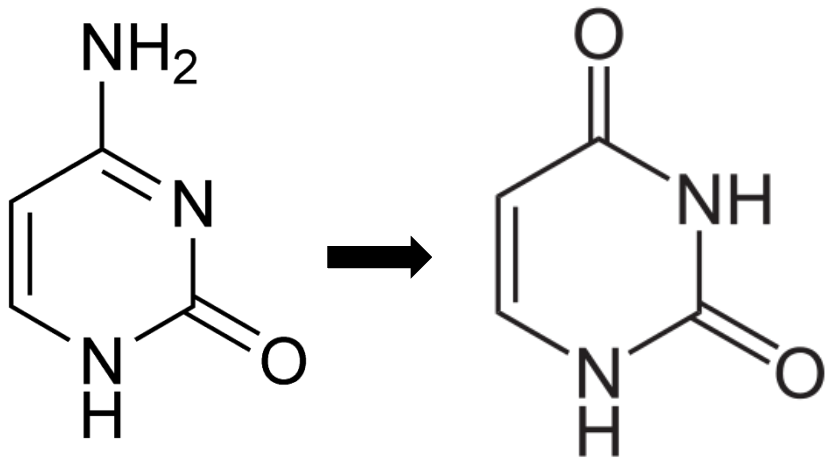
+ Fatores Ambientais: Raios UV, Radioatividade, Cigarro.....

Hidrólise (água)

Oxidação (EROs)

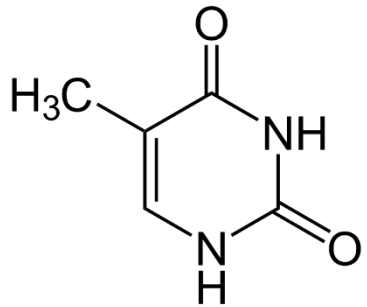
Metilação (SAM)

# Lesão vs mutação

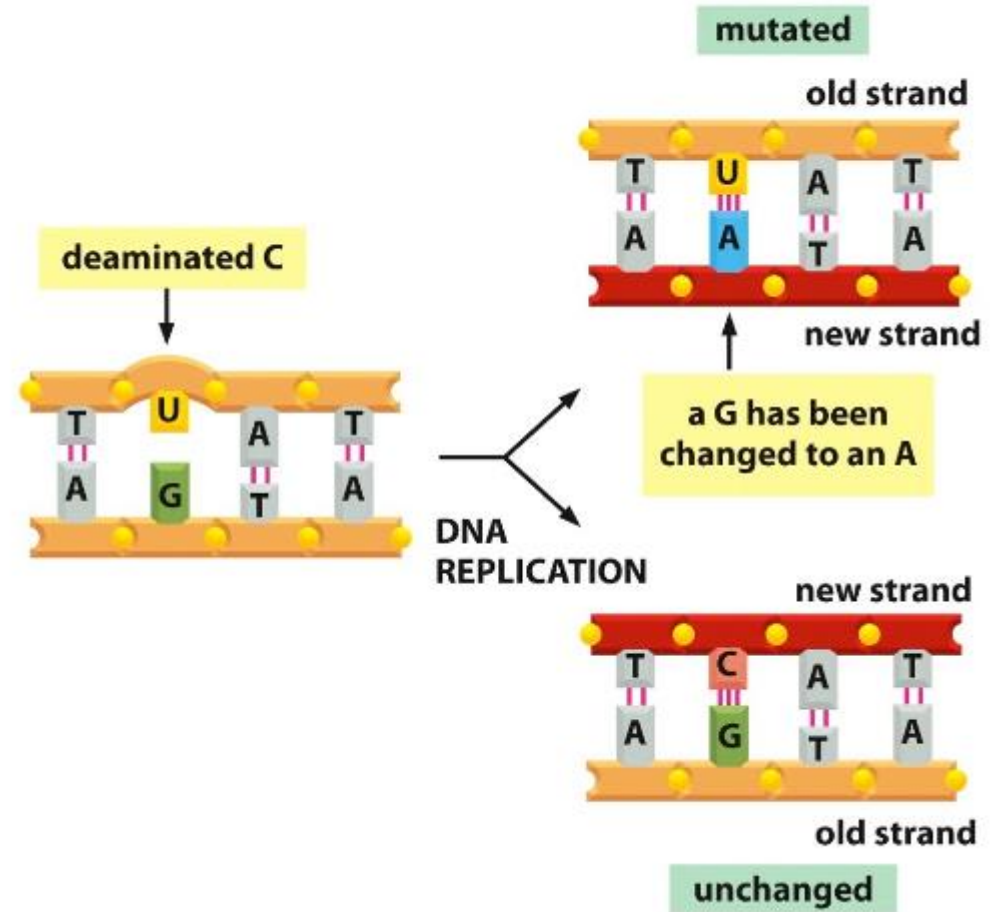


C

Uracila  
(U)



T



# Instabilidade Genômica em diferentes escalas

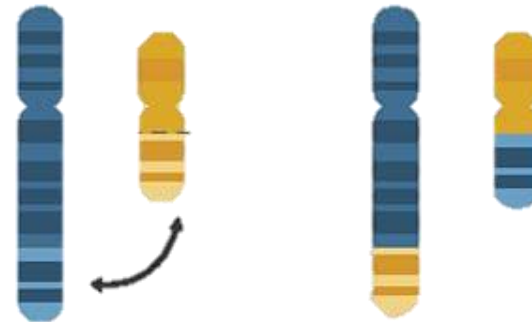
→ Mutação de ponto  
- transição vs transversão

ATGCAGTAGTAGCATG<sup>A</sup>CGTAGAGTACTGTGACGTA  
↓  
ATGCAGTAGTAGCATG<sup>G</sup>CGTAGAGTACTGTGACGTA

→ Inserção ou deleção

ATGCAGTAGTAGCATG<sup>A</sup>CGTAGAGTACTGTGACGTA  
↓  
ATGCAGTAGTAGCATG<sup>AG</sup>CGTAGAGTACTGTGACGTA

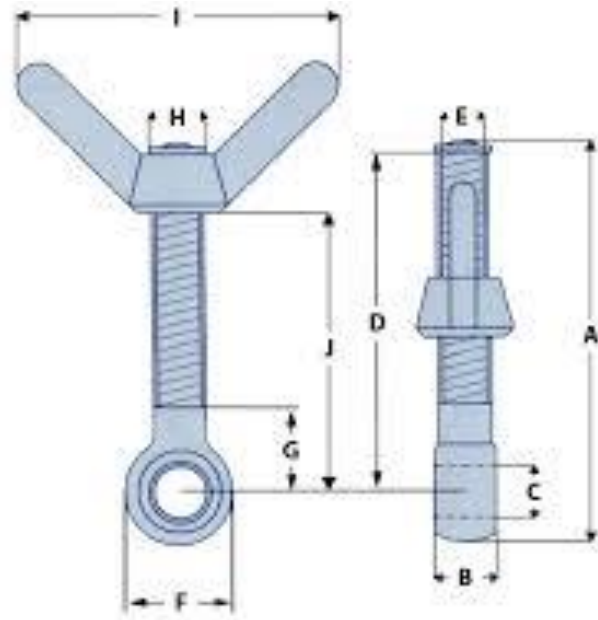
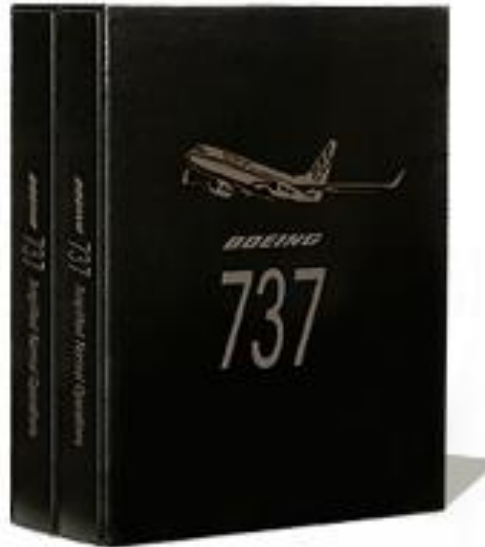
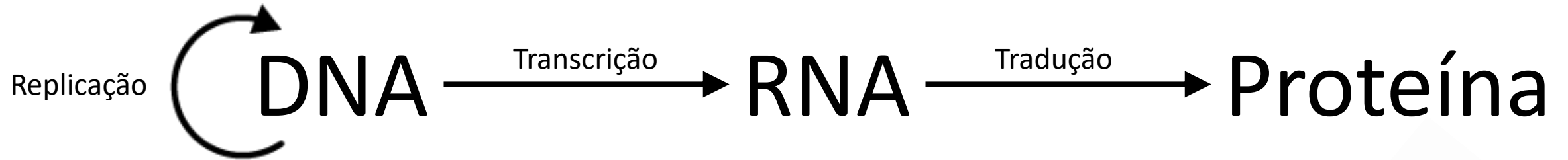
→ Aberrações Cromossômicas  
- inversão, translocação, duplicação



→ Aneuploidia



# Alterações no código genético são provavelmente prejudiciais



# Alterações no Código Genético

## Alterações Desvantajosas

Morte celular

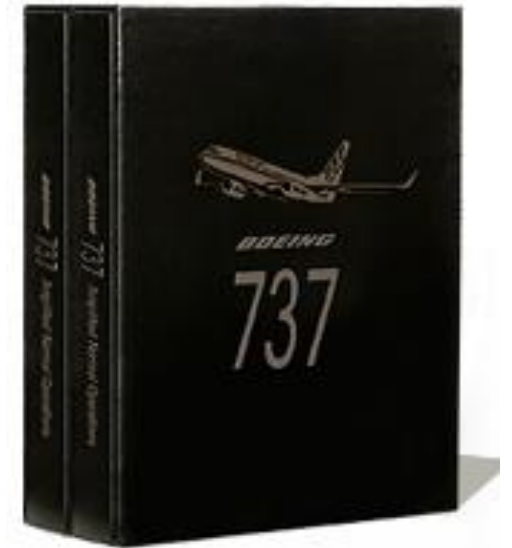
Senescência

Envelhecimento

## Alterações “Vantajosas”

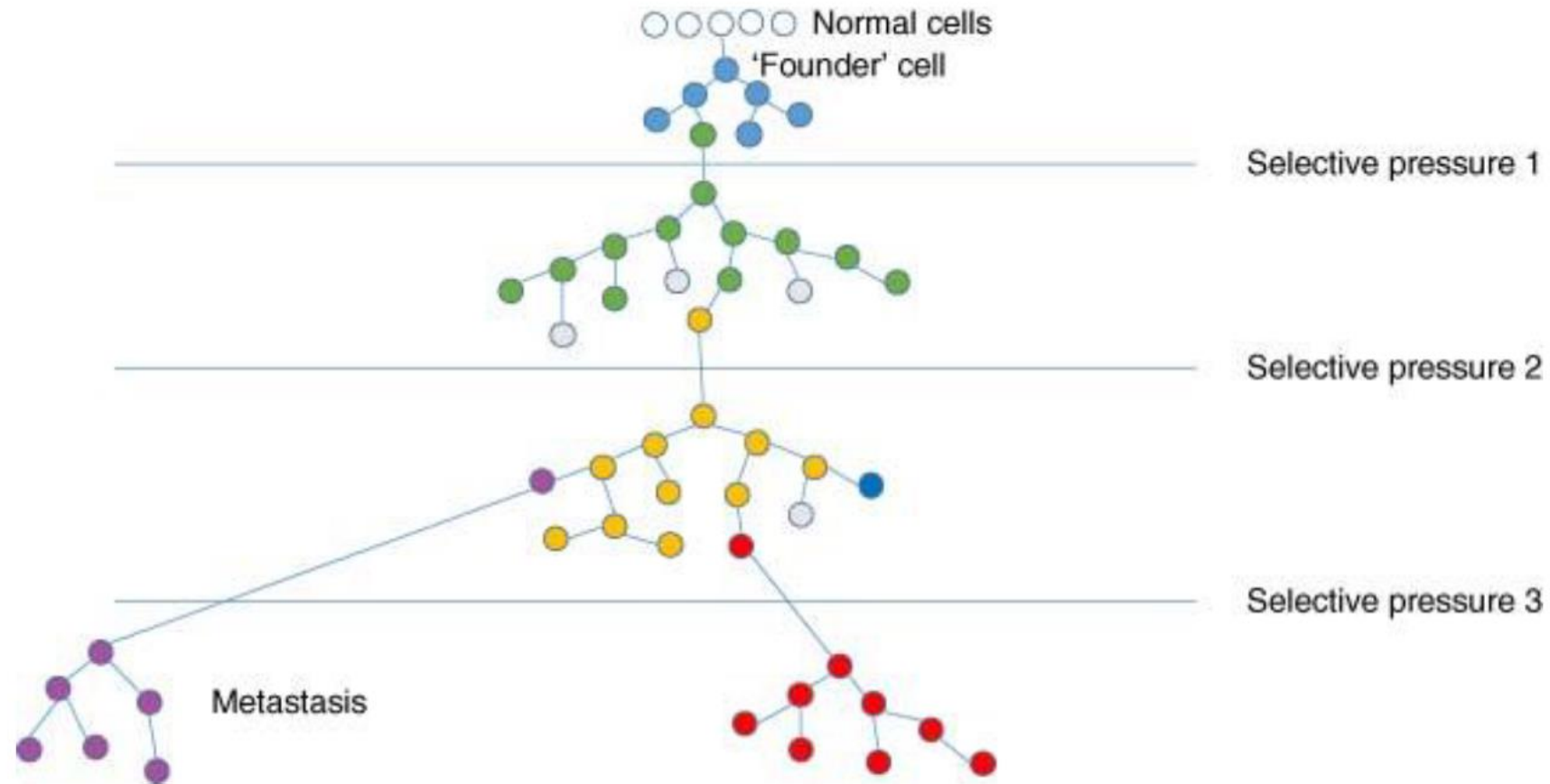
Evolução (unicelular ou células germinativas)

Câncer (células somáticas)

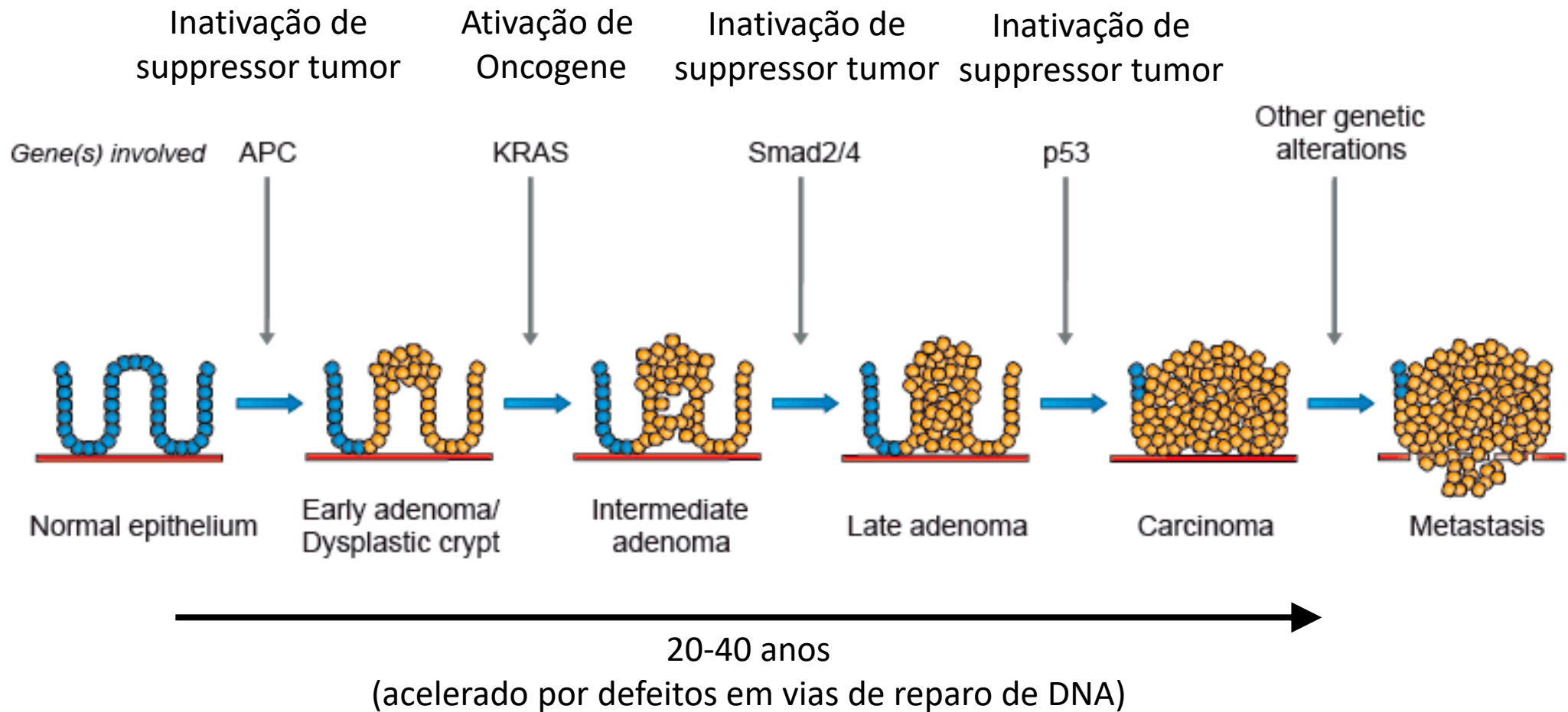




# O acúmulo de mutações favorece a evolução de tumores

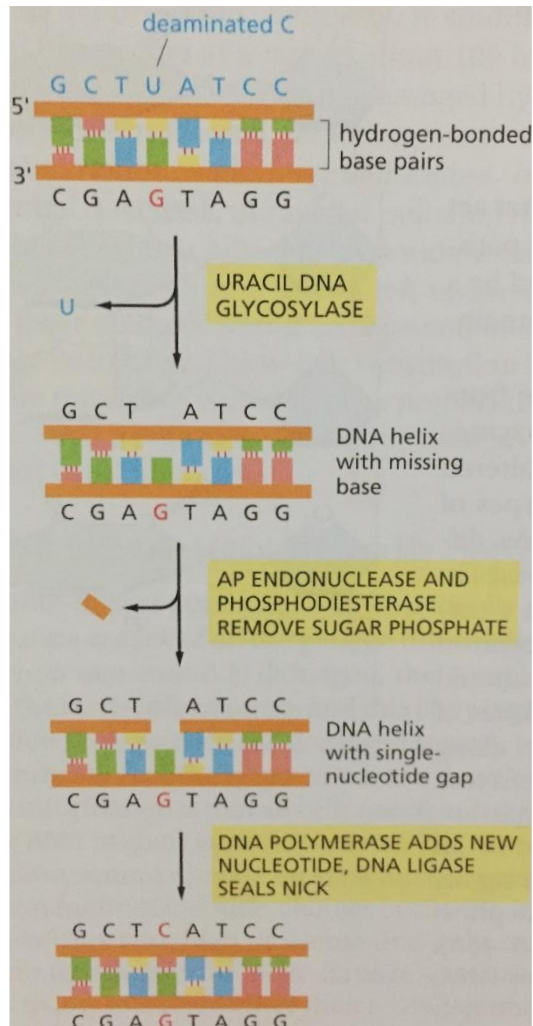


# O acúmulo de mutações favorece a evolução de tumores

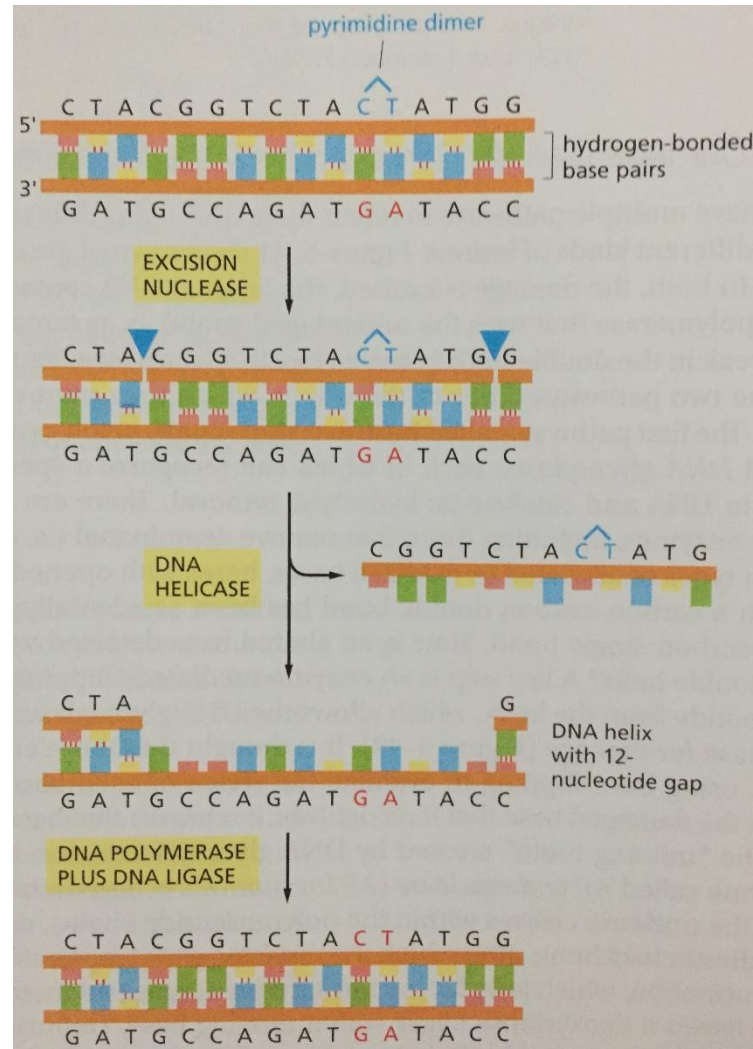


# A importância de ter duas fitas de DNA

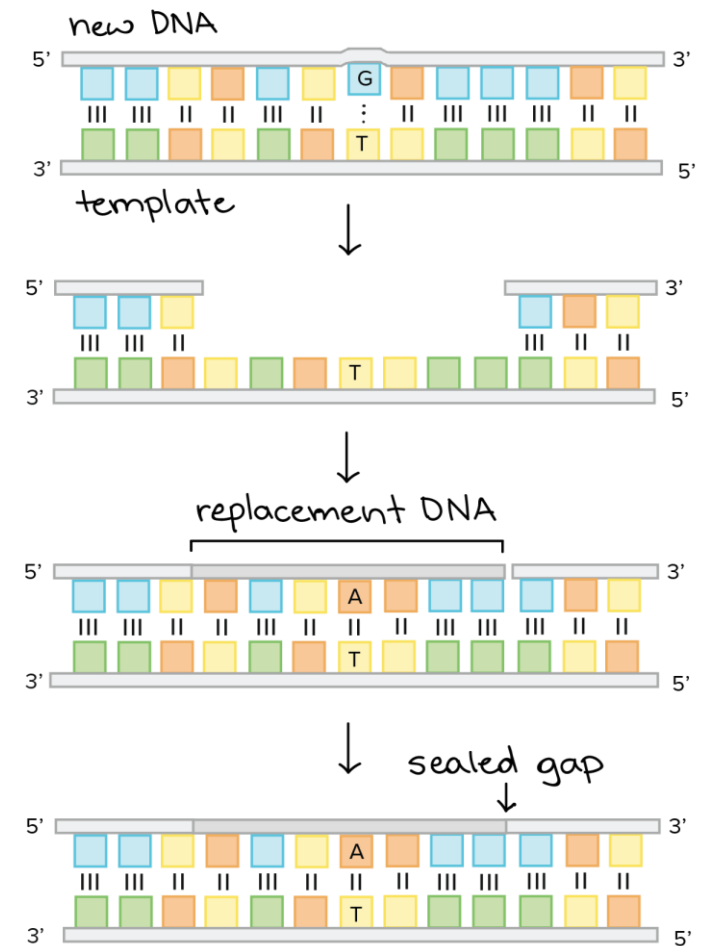
## BER



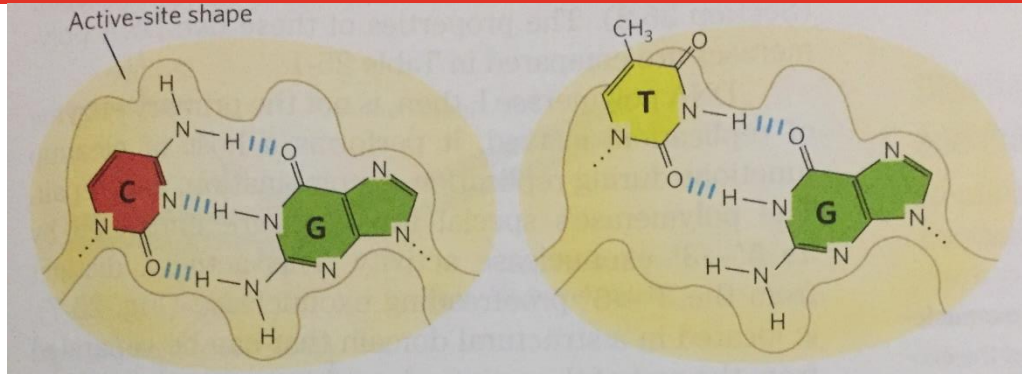
## NER



## MMR



# Mismatch repair contribui para fidelidade da replicação



1 erro a cada  $10^5$  pb

+ Mecanismo interno de correção (proofreading)

1 erro a cada  $10^2$

+ Mismatch repair (“vigilância”)

1 erro a cada  $10^3$

---

1 erro a cada  $10^{10}$

genoma *E.coli*  $4 \times 10^6$  pb

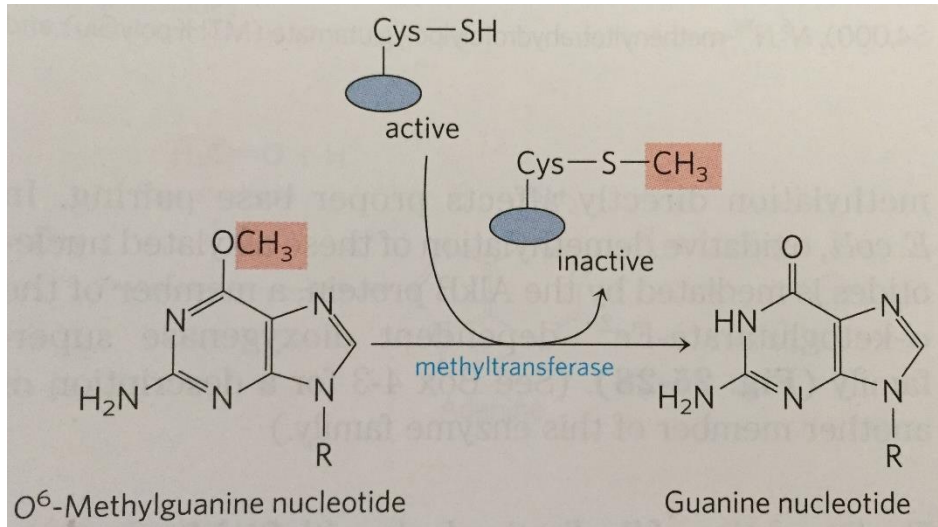
genoma humano  $3 \times 10^9$  pb

**TABLE 6-1 ERROR RATES**

US Postal Service on-time delivery of local first-class mail	13 late deliveries per 100 parcels
Airline luggage system	1 lost bag per 200
A professional typist typing at 120 words per minute	1 mistake per 250 characters
Driving a car in the United States	1 death per $10^4$ people per year
DNA replication (without mismatch repair)	1 mistake per $10^7$ nucleotides copied

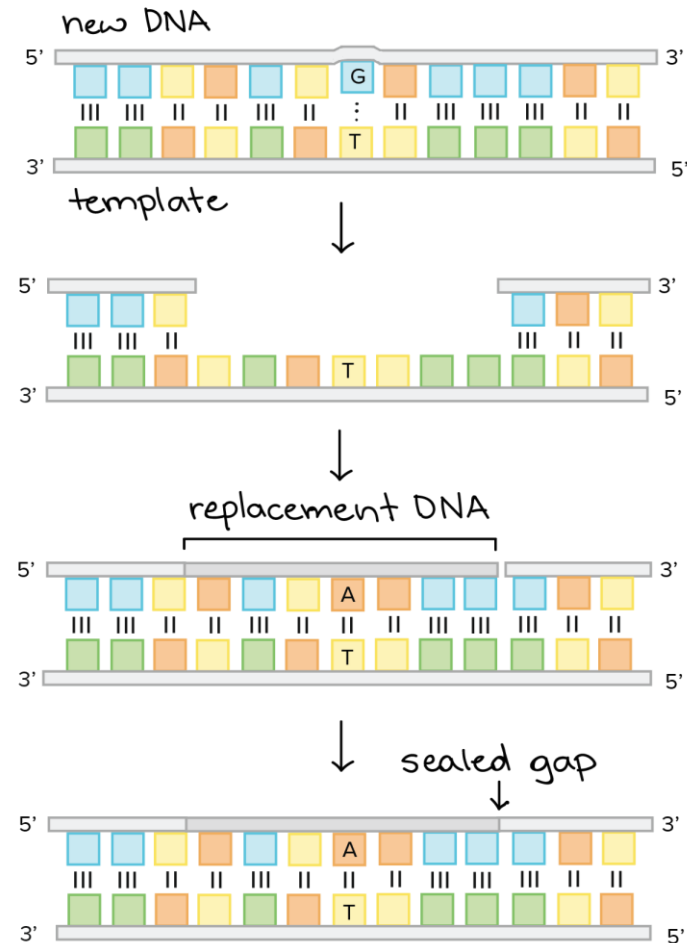
# A célula não economiza ATP para reparar DNA

## Reversão direta do dano



O<sup>6</sup>-Methylguanine methyltransferase (MGMT)

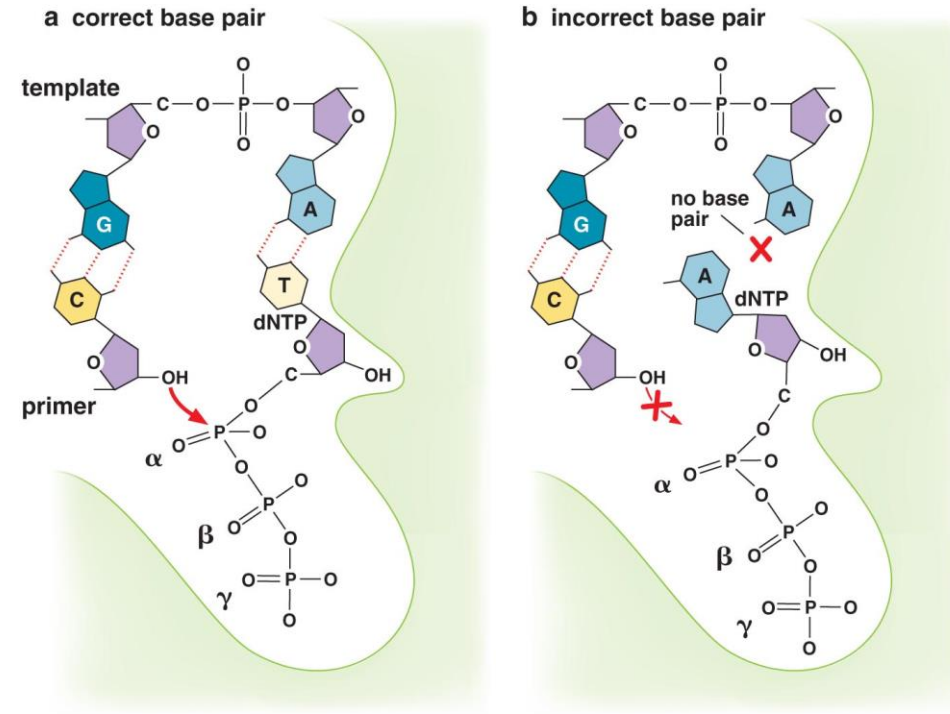
## Mismatch Repair (MMR)



# Síntese translesão

**TABLE 8-2** Activities and Functions of DNA Polymerases

Prokaryotic ( <i>E. coli</i> )	Number of Subunits	Function
Pol I	1	RNA primer removal, DNA repair
Pol II (Din A)	1	DNA repair
Pol III core	3	Chromosome replication
Pol III holoenzyme	9	Chromosome replication
Pol IV (Din B)	1	DNA repair, translesion synthesis (TLS)
Pol V (UmuC, UmuD' <sub>2</sub> C)	3	TLS
Eukaryotic	Number of Subunits	Function
Pol $\alpha$	4	Primer synthesis during DNA replication
Pol $\beta$	1	Base excision repair
Pol $\gamma$	3	Mitochondrial DNA replication and repair
Pol $\delta$	2-3	Lagging-strand DNA synthesis; nucleotide and base excision repair
Pol $\epsilon$	4	Leading-strand DNA synthesis; nucleotide and base excision repair
Pol $\theta$	1	DNA repair of cross-links
Pol $\zeta$	1	TLS
Pol $\lambda$	1	Meiosis-associated DNA repair
Pol $\mu$	1	Somatic hypermutation
Pol $\kappa$	1	TLS
Pol $\eta$	1	Relatively accurate TLS past <i>cis-syn</i> cyclobutane dimers
Pol $\iota$	1	TLS, somatic hypermutation
Rev1	1	TLS



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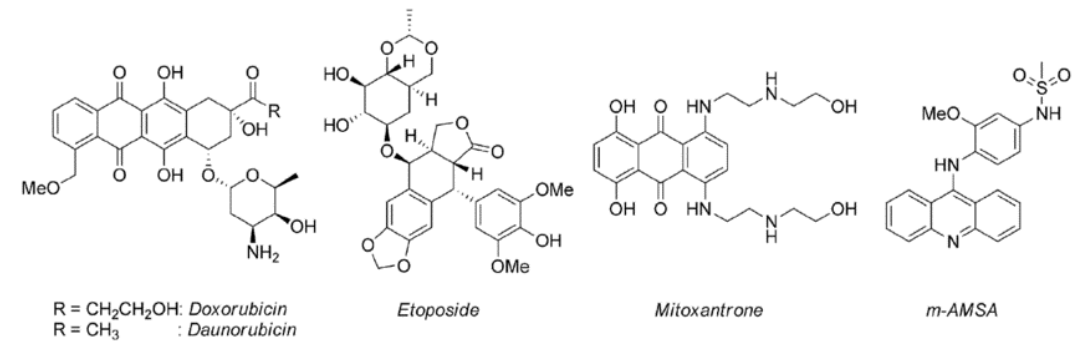
Relaxamento do sítio ativo para acomodar DNA danificado

# Quebras de fita dupla

Radiação ionizante



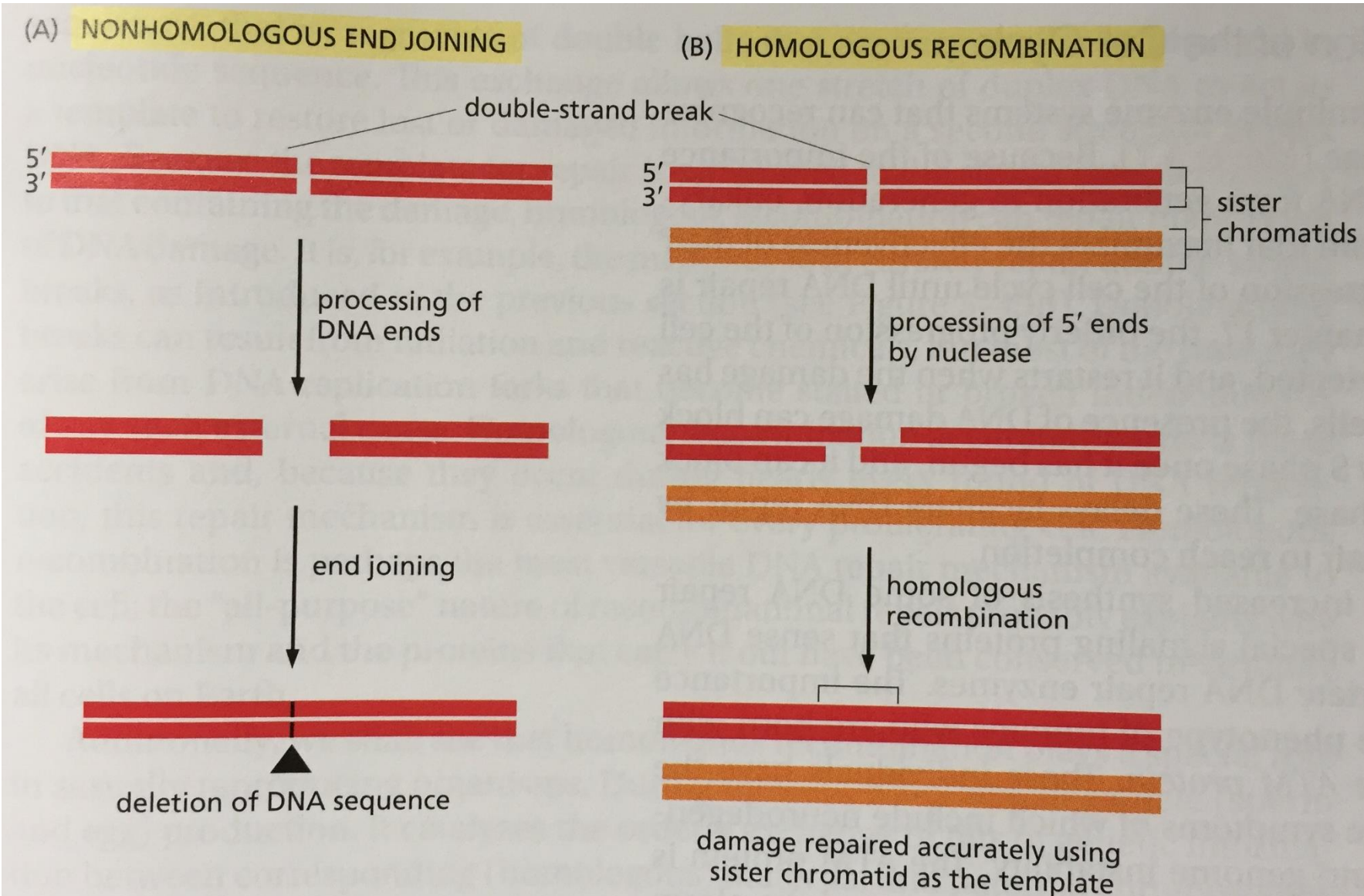
Top2 "poisons"



Replicação de quebras de fita simples



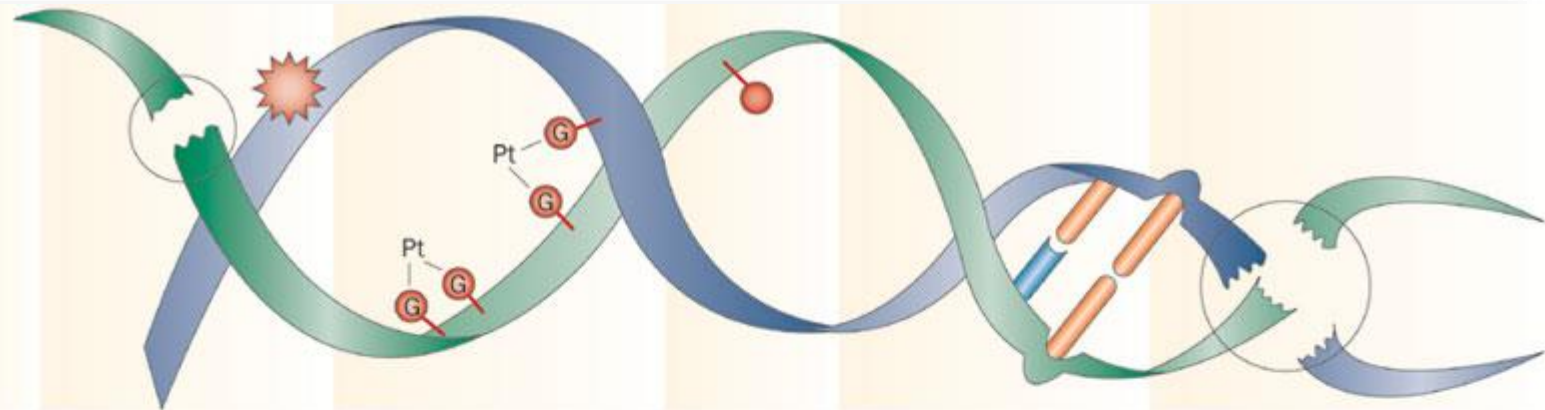
# Duas vias para reparo de quebras de fita dupla



Quando a célula tem uma cópia homóloga para usar?



# Reparo de DNA e doenças genéticas raras



DNA lesion	Single-strand break Single-base damage	Bulky lesions Crosslinks	O <sup>6</sup> MeG	Mismatch	Double-strand break	
Repair pathway	BER	NER GG-NER TC-NER	DR	MMR	HR	NHEJ
Proteins involved/biomarkers	<p><b>X</b></p> <p>OGG1 XPC hHR23F PCNA Pol β FEN 1 Ligase III</p>	<p><b>X</b></p> <p>XPD DDB1 CSB XPC PCNA Pol δ Pol ε Ligase I</p>	<p>AGT</p> <p>PCNA Pol δ Ligase I Ligase IV</p>	<p><b>X</b></p> <p>hHR23F PCNA Pol δ Ligase I Ligase IV</p>	<p><b>X</b></p> <p>BRCA1/2 FANCD1 FANCD2 PCNA Pol δ Pol ε Ligase I</p>	<p><b>X</b></p> <p>KU80 DNA-PKcs XRCC4-XLF PCNA Pol μ Ligase IV</p>

Neurodegeneração  
Predisposição a câncer

Predisposição a câncer de pele  
(Xeroderma Pigmentosum)

Predisposição a câncer colorretal  
(Síndrome de Lynch)

Predisposição a câncer de mama  
(BRCA1/BRCA2)

Falência da medula óssea  
(Anemia de Fanconi)

Defeitos no desenvolvimento  
neurológico (Microcefalia)

Imunodeficiência (SCID)

# Aula que vem: CRISPR/Cas9

