

A stylized illustration of a repair center. The building is blue with a purple roof. It has a brown door with a small white square window and a four-pane window above it. A yellow oval sign on two poles above the building reads "REPAIR CENTER". The building is set on a pinkish-red hill against a light blue sky.

REPAIR CENTER

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Para quê estudar reparo do DNA?

Principais especialidades envolvidas:

- **Oncologia (Clínica Médica, Cirurgia, Pediatria)**
- **Geriatria**
- **Dermatologia**
- **Neurologia**
- **Imunologia**
- **Endocrinologia**
- **Oftalmologia**
- **...**

Indústria farmacêutica (teste de novas drogas)

Novas terapias (CRISPR)

Quais os principais mecanismos de reparo do DNA?

(slide da Profa. Aparecida)

	Tipos de Dano	Principal Mecanismo de Reparo
1	Base modificada quimicamente (oxidação, desaminação, metilação etc.)	BER - Reparo por excisão de base
	Deleção de uma base (sítio apurínico ou apurimidínico)	
	Quebra de fita-única de DNA	
	Distorção da dupla-hélice (dímeros de pirimidina)	NER - Reparo por excisão de nucleotídeo
2	Ligação cruzada intra-cadeia	

Quais os principais mecanismos de reparo do DNA?

(slide da Profa. Aparecida)

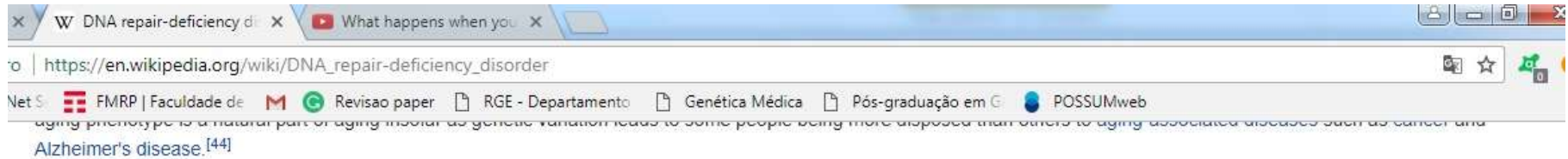
	Tipos de Dano	Principal Mecanismo de Reparo
3	Base malpareada por erros na replicação do DNA	MMR - Reparo por malpareamento
	Pequenas inserções ou deleções devido ao deslocamento durante a replicação	
4	Quebra na fita dupla de DNA	HR - recombinação homóloga
		NHEJ - Junção das extremidades não homólogas

Principais Mecanismos de Reparo

- Reparo por excisão de base
- Reparo por excisão de nucleotídeo
- Reparo por malpareamento (mismatch)
- Recombinação homóloga
- Junção das extremidades (pontas) não homólogas

Obs: há outros!

Gene, doença, mecanismo de reparo



DNA repair defects and increased cancer risk [\[edit \]](#)

Individuals with an inherited impairment in DNA repair capability are often at increased risk of cancer.^[45] When a mutation is present in a DNA repair gene, the repair gene will either not be expressed or be expressed in an altered form. Then the repair function will likely be deficient, and, as a consequence, damages will tend to accumulate. Such DNA damages can cause errors during DNA synthesis leading to mutations, some of which may give rise to cancer. Germ-line DNA repair mutations that increase the risk of cancer are listed in the Table.

Inherited DNA repair gene mutations that increase cancer risk

DNA repair gene	Protein	Repair pathways affected	Cancers with increased risk
breast cancer 1 & 2	BRCA1 BRCA2	HRR of double strand breaks and daughter strand gaps ^[46]	breast, ovarian ^[47]
ataxia telangiectasia mutated	ATM	Different mutations in <i>ATM</i> reduce HRR, SSA or NHEJ ^[48]	leukemia, lymphoma, breast ^{[48][49]}
Nijmegen breakage syndrome	NBS (NBN)	NHEJ ^[50]	lymphoid cancers ^[50]
MRE11A	MRE11	HRR and NHEJ ^[51]	breast ^[52]
Bloom syndrome	BLM (helicase)	HRR ^[53]	leukemia, lymphoma, colon, breast, skin, lung, auditory canal, tongue, esophagus, stomach, tonsil, larynx, uterus ^[54]
WRN	WRN	HRR, NHEJ, long patch BER ^[55]	soft tissue sarcoma, colorectal, skin, thyroid, pancreas ^[56]

**Resumo bem simplificado – fácil de entender
(lembre-se dele nas outras partes do GD)**

<https://www.youtube.com/watch?v=vP8-5Bhd2ag>

Geral – Enzimas Importantes

Helicase

Endonuclease

Exonuclease

Polimerase

Ligase

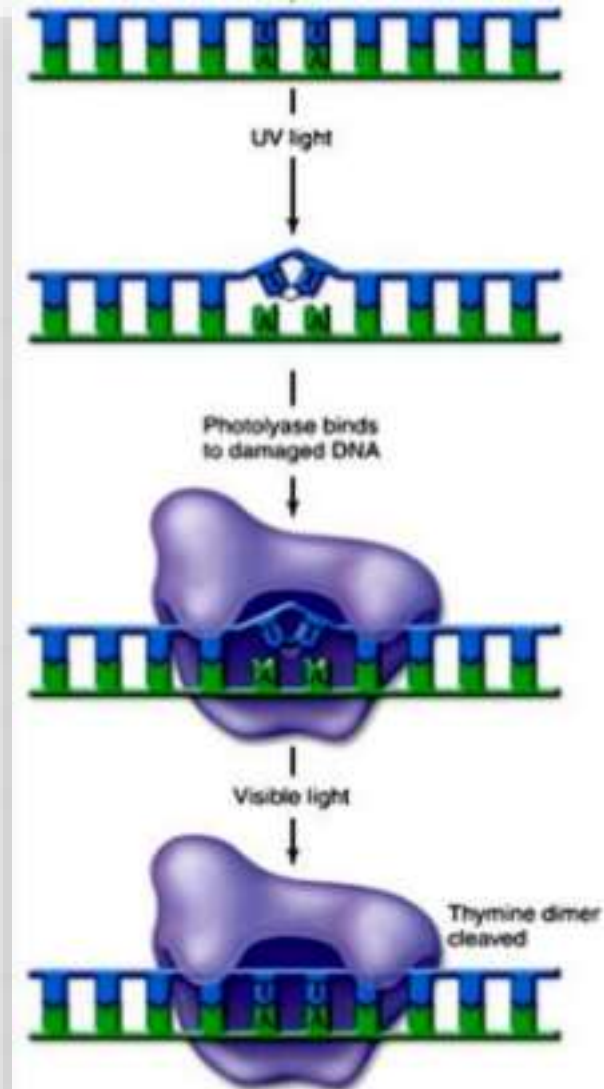
REPARO DIRETO: FOTOREATIVAÇÃO

(slide da Profa. Aparecida)

- São processos celulares que reparam dímeros de timina induzidos pela UV.

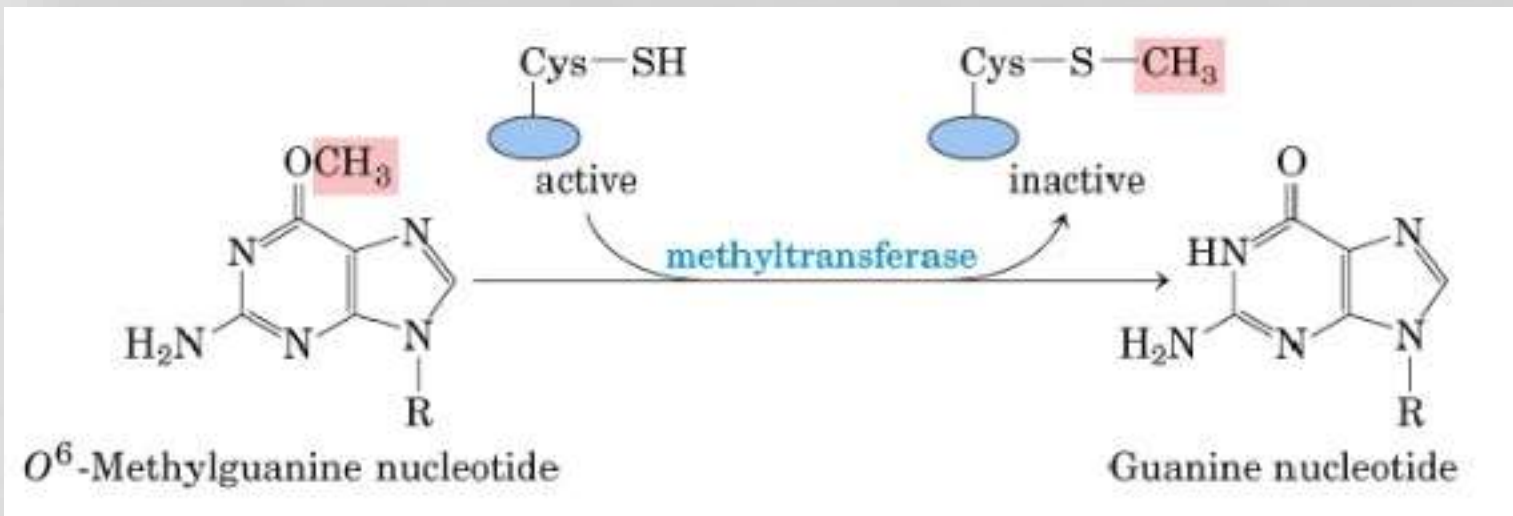
FOTOLIASE

Não ocorre em humanos



REPARO DIRETO: REMOÇÃO

(slide da Profa. Aparecida)



MGMT

O⁶-methylguanine DNA
methyltransferase

Um pequeno dano de base é detectado e reparado por meio do reparo por excisão de base

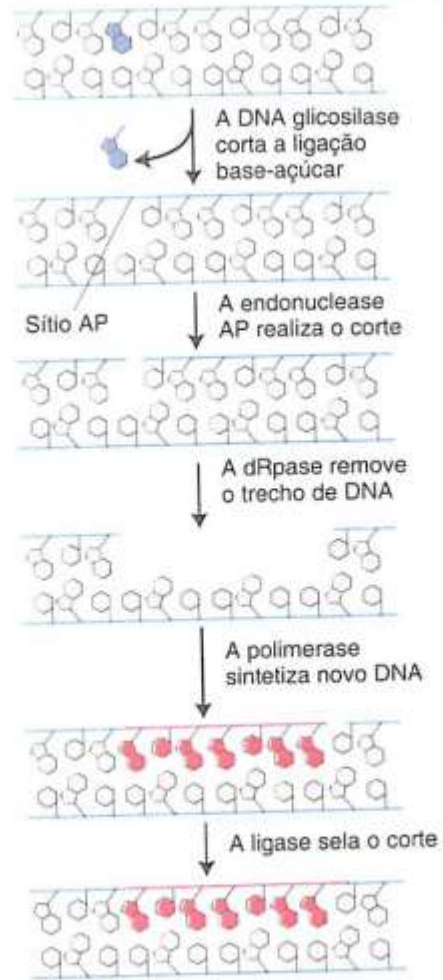


FIGURA 16.20 No reparo por excisão de base, as bases danificadas são removidas e reparadas por meio da ação sequencial de uma DNA glicosilase, uma endonuclease AP, uma desoxirribosfosfodiesterase (dRpase), uma DNA polimerase e uma ligase.

Principais doenças e seus mecanismos de reparo

DNA REPAIR/DNA DAMAGE RESPONSE SYSTEM	SINGLE-GENE DISORDERS	DISEASE FEATURES ^a			
		C	P	N	I
Mismatch repair	hereditary nonpolyposis colorectal cancers (Lynch syndrome)	+	-	-	-
Nucleotide excision repair (NER)	xeroderma pigmentosum	+	-	+	-
NER (transcription-coupled repair)	Cockayne syndrome	-	+	+	-
	trichothiodystrophy	-	+	+	-
Single-strand break (SSB) repair	ataxia oculomotor apraxia 1	-	-	+	-
	spinocerebellar ataxia with axonal neuropathy 1	-	-	+	-
Interstrand cross-link repair	Fanconi anemia	+	+	+	+
Double-strand break (DSB) repair (NHEJ)	Lig4 syndrome	+	-	+	+
	severe combined immunodeficiency	-	-	-	+
DNA damage signaling/DSB repair	ataxia telangiectasia	+	-	+	+
	Seckel syndrome	-	-	+	+
	primary microcephaly 1	-	-	+	-
Homologous recombination (HR)	Bloom syndrome	+	-	+	+
Telomere maintenance (TM)	dyskeratosis congenita	+	+	+	+
Base excision repair (BER) in mtDNA	spinocerebellar ataxia–epilepsy	-	-	+	-
	progressive external ophthalmoplegia	-	-	-	-
HR, BER, TM	Werner syndrome	+	+	-	-

Table 1 Examples of inherited disorders of DNA repair/DNA damage responses. ^aC, cancer susceptibility; P, progeria;

N, neurological features; I, immunodeficiency.

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	spinocerebellar ataxia with axonal neuropathy 1	-	-	+	-
Interstrand cross-link repair	Fanconi anemia	+	+	+	+
Double-strand break (DSB) repair (NHEJ)	Lig4 syndrome	+	-	+	+
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	Seckel syndrome	-	-	+	+
	primary microcephaly 1	-	-	+	-
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Base excision repair (BER) in mtDNA	spinocerebellar ataxia–epilepsy	-	-	+	-
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Table 1 Examples of inherited disorders of DNA repair/DNA damage responses. ^aC, cancer susceptibility; P, progeria;

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Xeroderma Pigmentoso

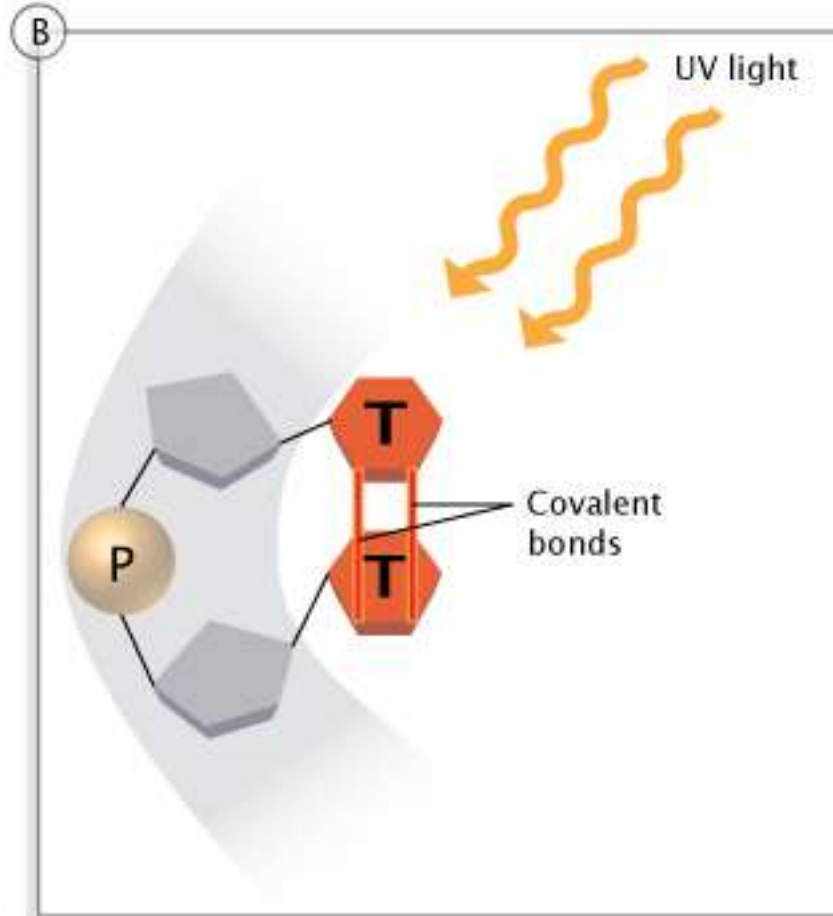
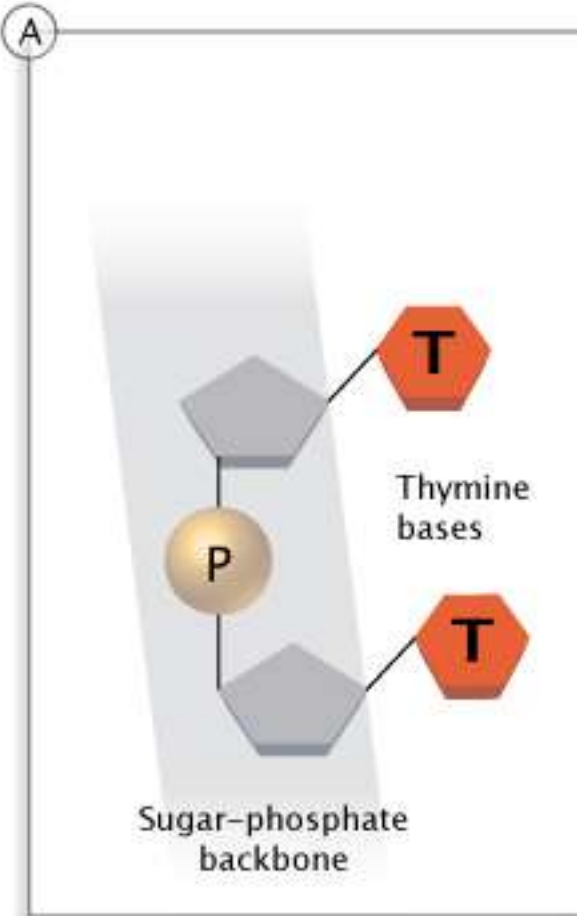
**Prof. Dr. Menk – Instituto Biociências – USP –
População Brasileira**

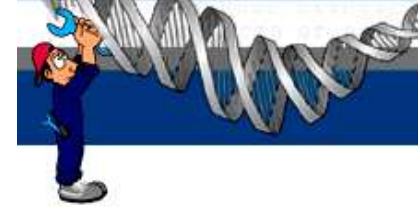
<https://www.youtube.com/watch?v=uKqCXTbmwul>

Ver OMIM

FORMAÇÃO DE DÍMEROS DE PIRIMIDINA

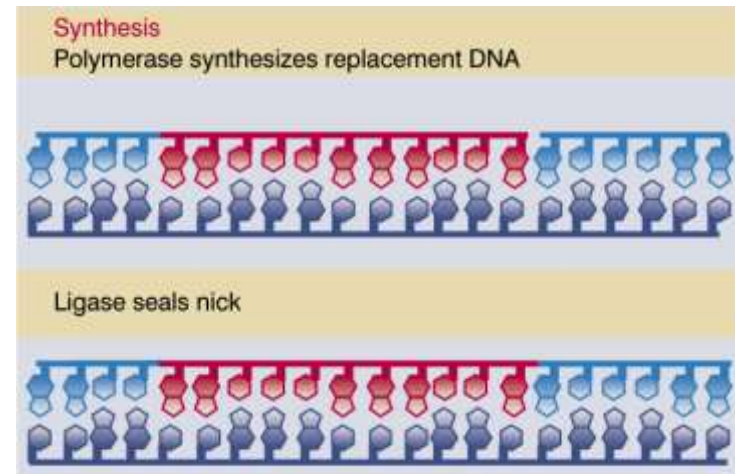
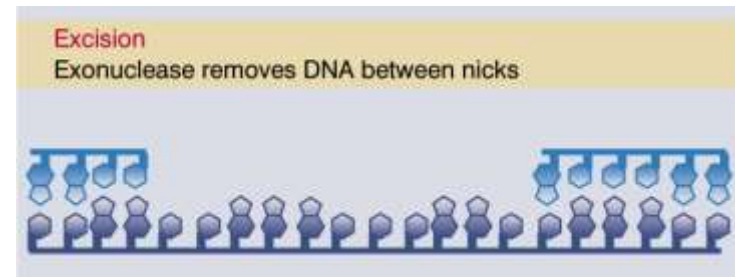
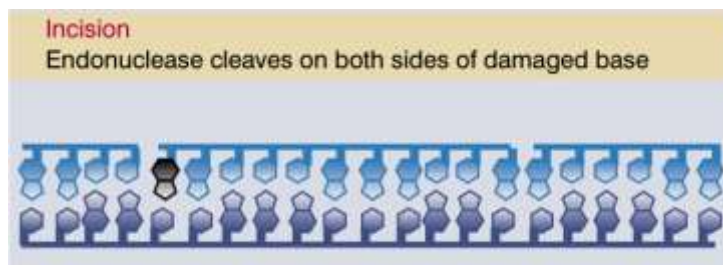
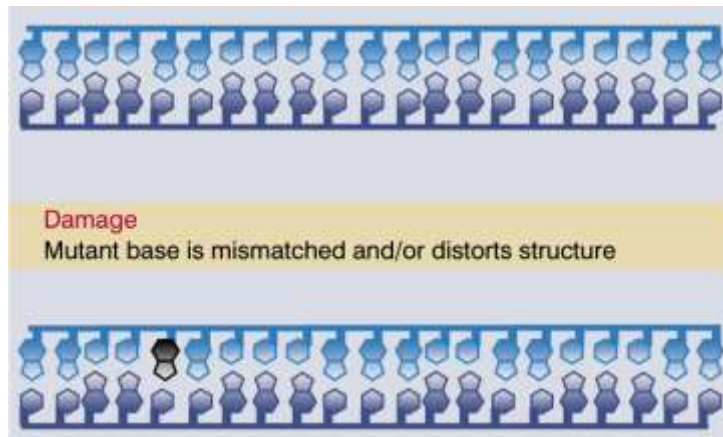
(slide da Profa. Aparecida)





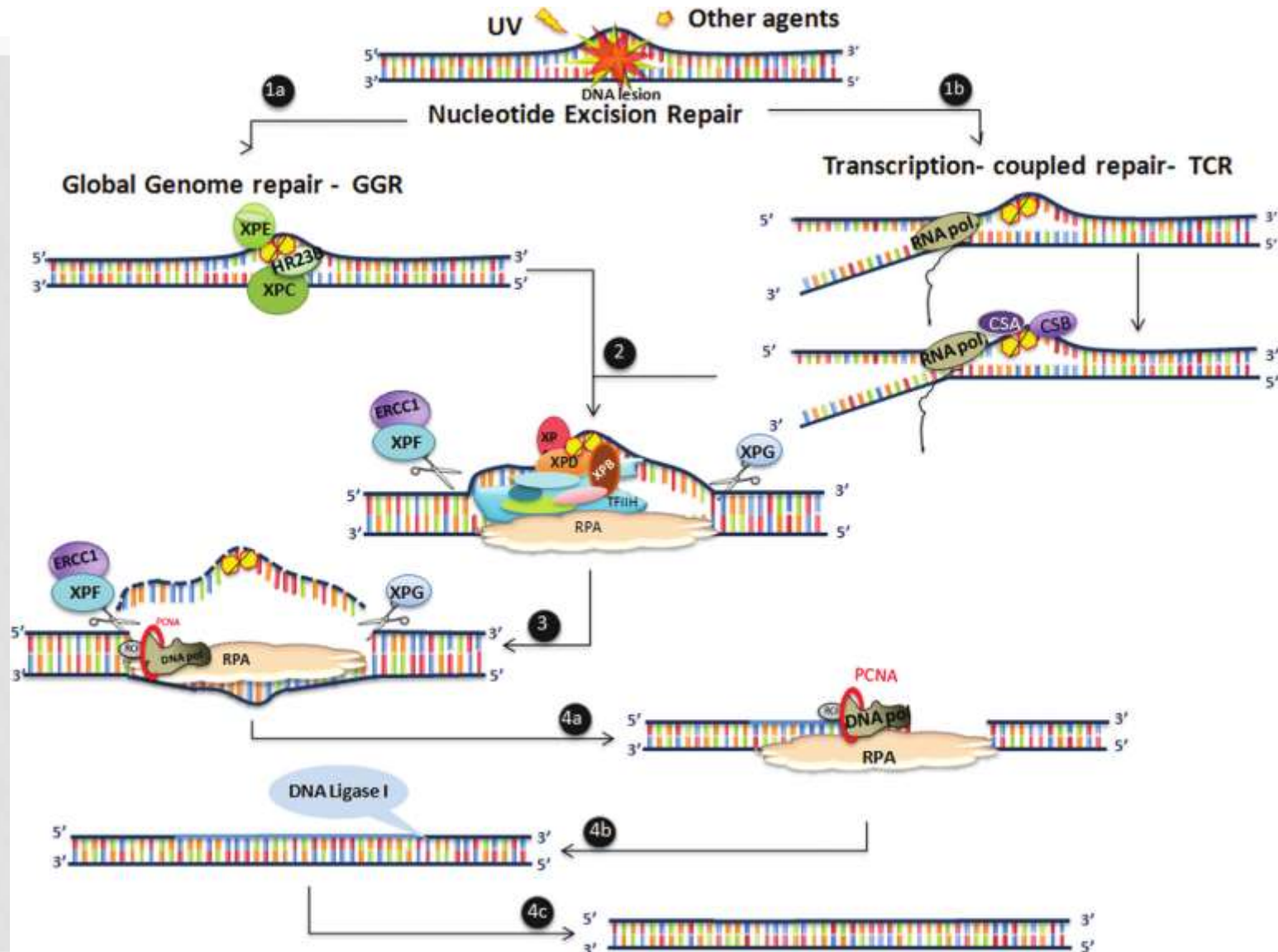
Reparação por Excisão de Nucleotídeo (REN)

1. Reconhecimento da lesão
2. Incisão da fita lesada em ambos os lados da lesão
3. Excisão do segmento contendo a lesão
4. Síntese do novo segmento de DNA e Ligação



NUCLEOTÍDEO EXCISION REPAIR (NER)

(slide da Profa. Aparecida)



[http://highered.mheducation.com/sites/
dl/free/0072835125/126997/animation33.
html](http://highered.mheducation.com/sites/dl/free/0072835125/126997/animation33.html)

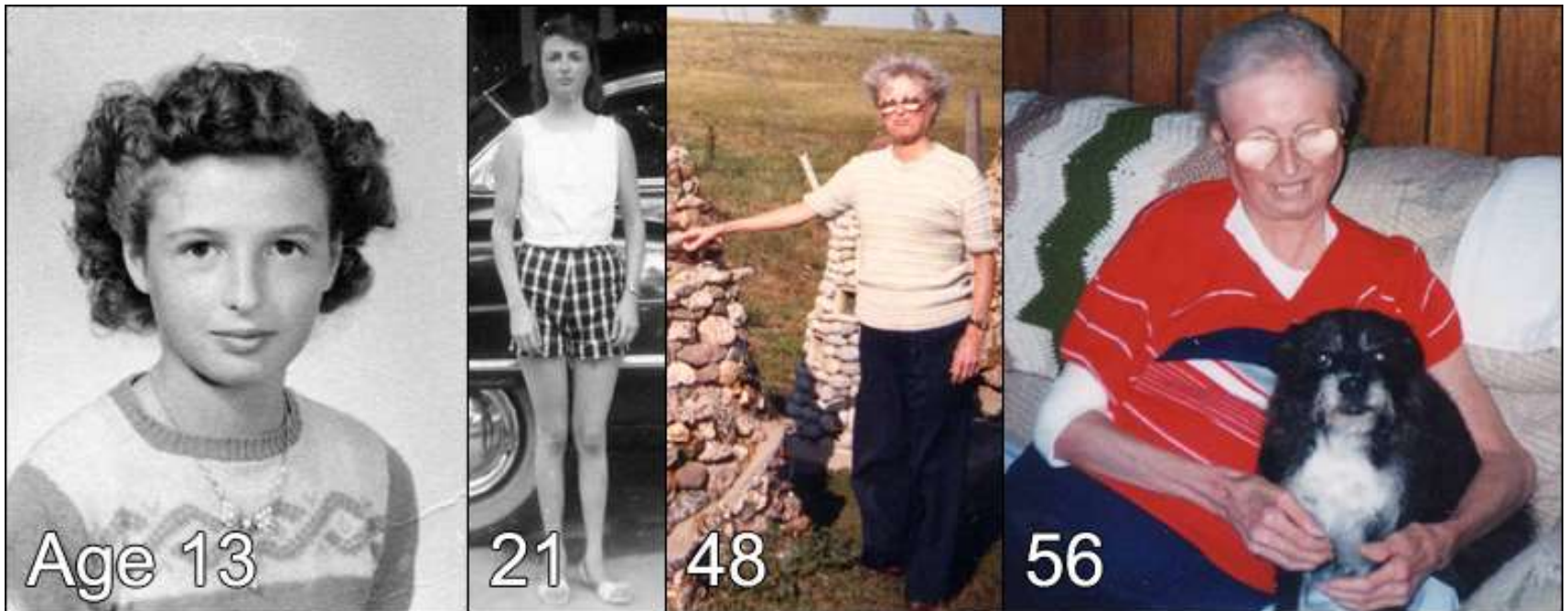
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NER (transcription-coupled repair)	Cockayne syndrome	-	+	+	-
	trichothiodystrophy	-	+	+	-
Single-strand break (SSB) repair	ataxia oculomotor apraxia 1	-	-	+	-
	spinocerebellar ataxia with axonal neuropathy 1	-	-	+	-
Interstrand cross-link repair	Fanconi anemia	+	+	+	+
Double-strand break (DSB) repair (NHEJ)	Lig4 syndrome	+	-	+	+
	severe combined immunodeficiency	-	-	-	+
DNA damage signaling/DSB repair	ataxia telangiectasia	+	-	+	+
	Seckel syndrome	-	-	+	+
	primary microcephaly 1	-	-	+	-
Homologous recombination (HR)	Bloom syndrome	+	-	+	+
Telomere maintenance (TM)	dyskeratosis congenita	+	+	+	+
Base excision repair (BER) in mtDNA	spinocerebellar ataxia–epilepsy	-	-	+	-
	progressive external ophthalmoplegia	-	-	-	-
HR, BER, TM	Werner syndrome	+	+	-	-

Table 1 Examples of inherited disorders of DNA repair/DNA damage responses. ^aC, cancer susceptibility; P, progeria;

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Síndrome de Wener

- “Progéria do adulto”
- **CUIDADO** para não confundir com outras síndromes progeroides (síndrome de Hutchinson-Gilford, síndrome de Cockaine). Esse erro é muito comum de se ver em aulas e na Internet.
- Várias alterações de reparo
- **OMIM**

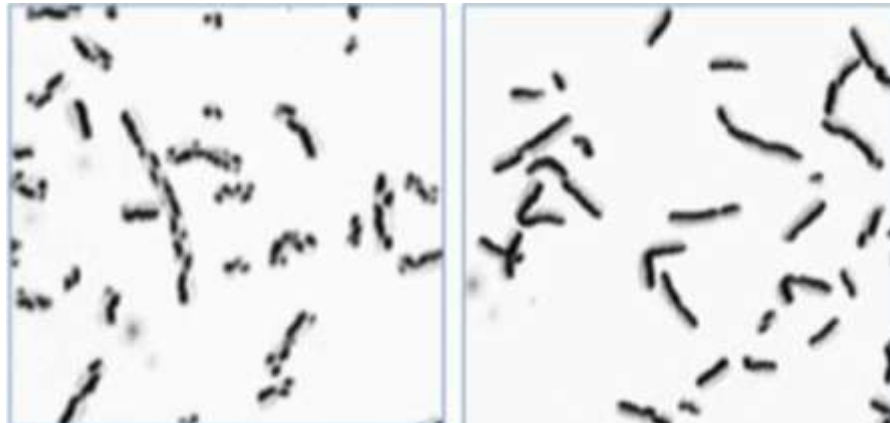


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Interstrand cross-link repair	Fanconi anemia	+	+	+	+
Double-strand break (DSB) repair (NHEJ)	Lig4 syndrome	+	-	+	+
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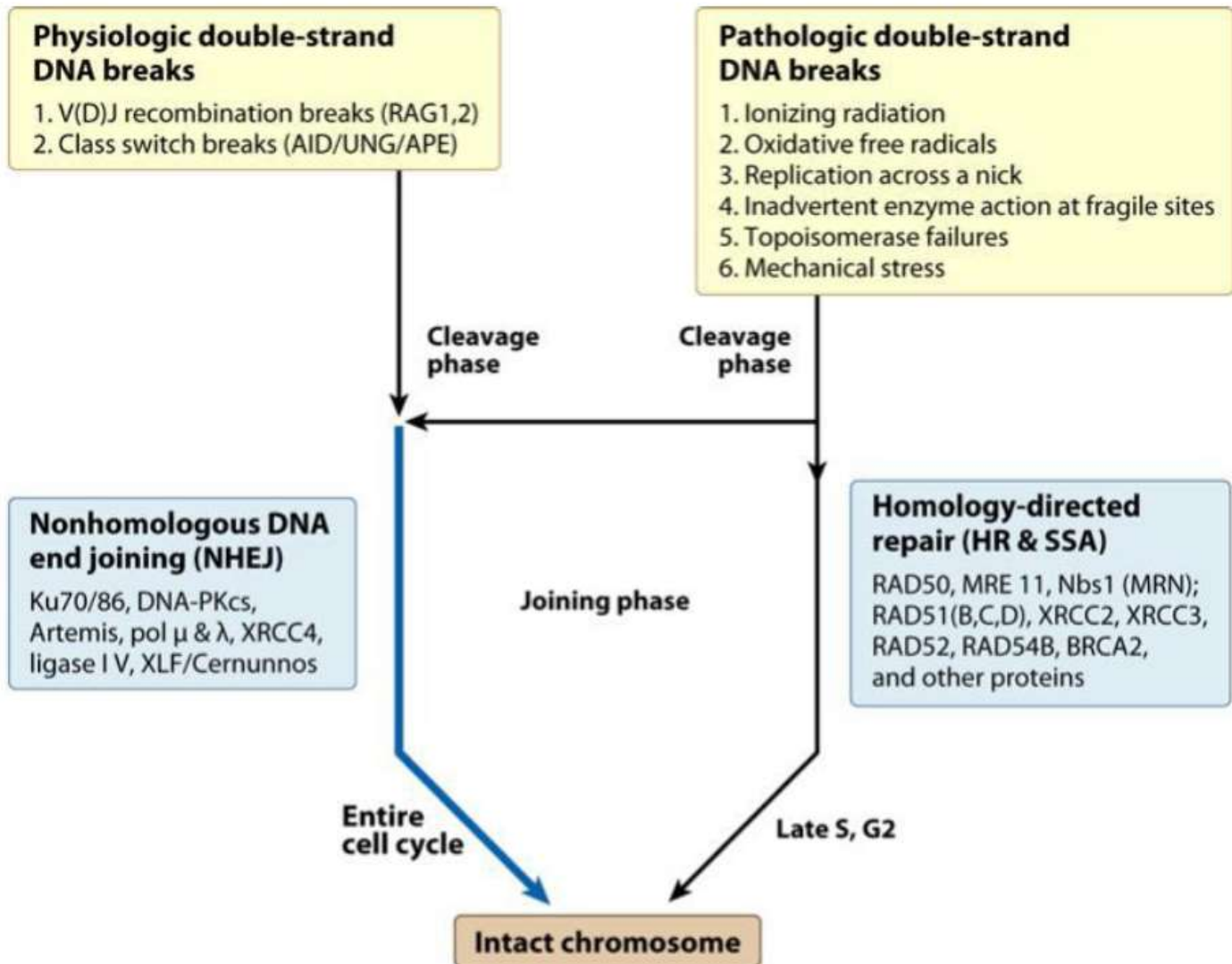
Síndrome de Bloom



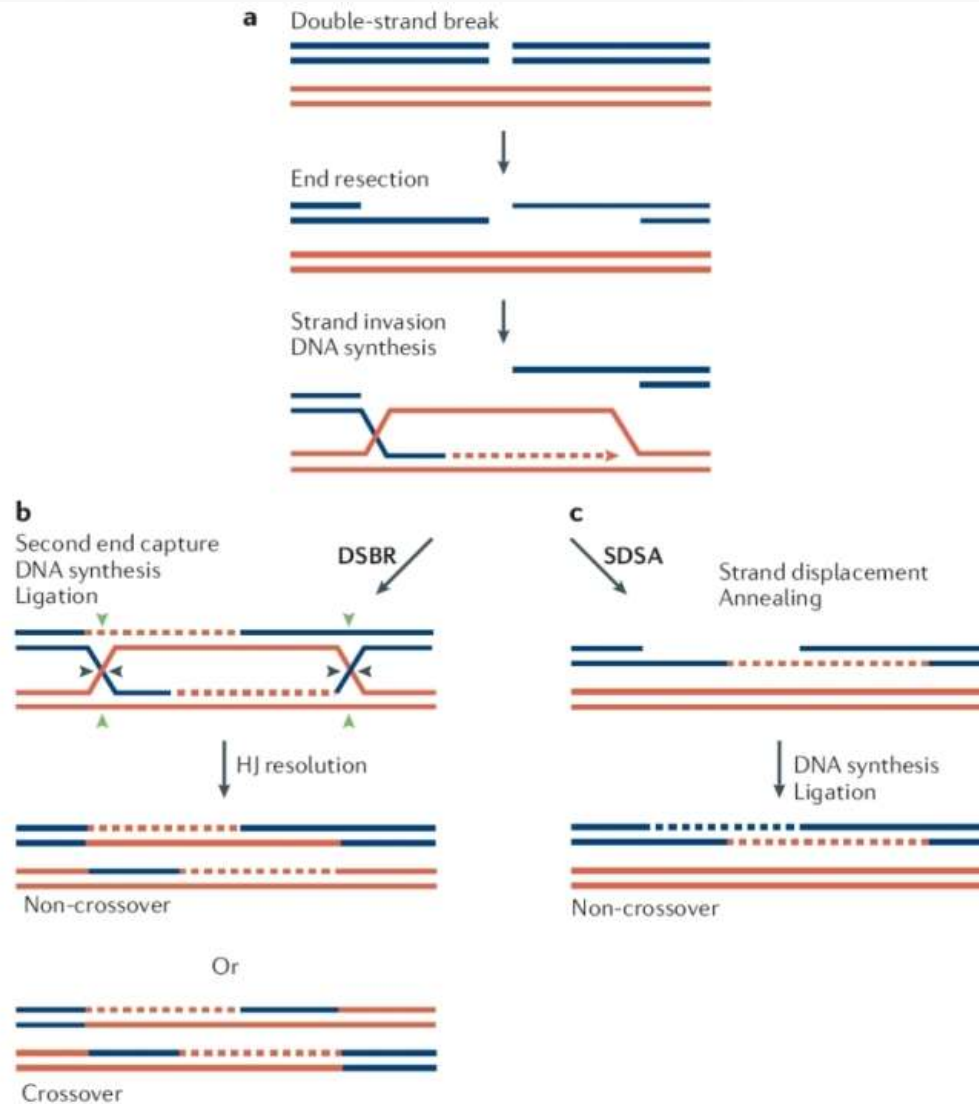
Troca de cromátides irmãs

REPARO POR RECOMBINAÇÃO HOMÓLOGA

(SLIDE DA PROFA. APARECIDA)



REPARO POR RECOMBINAÇÃO HOMÓLOGA (SLIDE DA PROFA. APARECIDA)



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Base excision repair (BER) in mtDNA	spinocerebellar ataxia-epilepsy	-	-	+	-
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HR, BER, TM	Werner syndrome	+	+	-	-

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SINDROME DE LYNCH

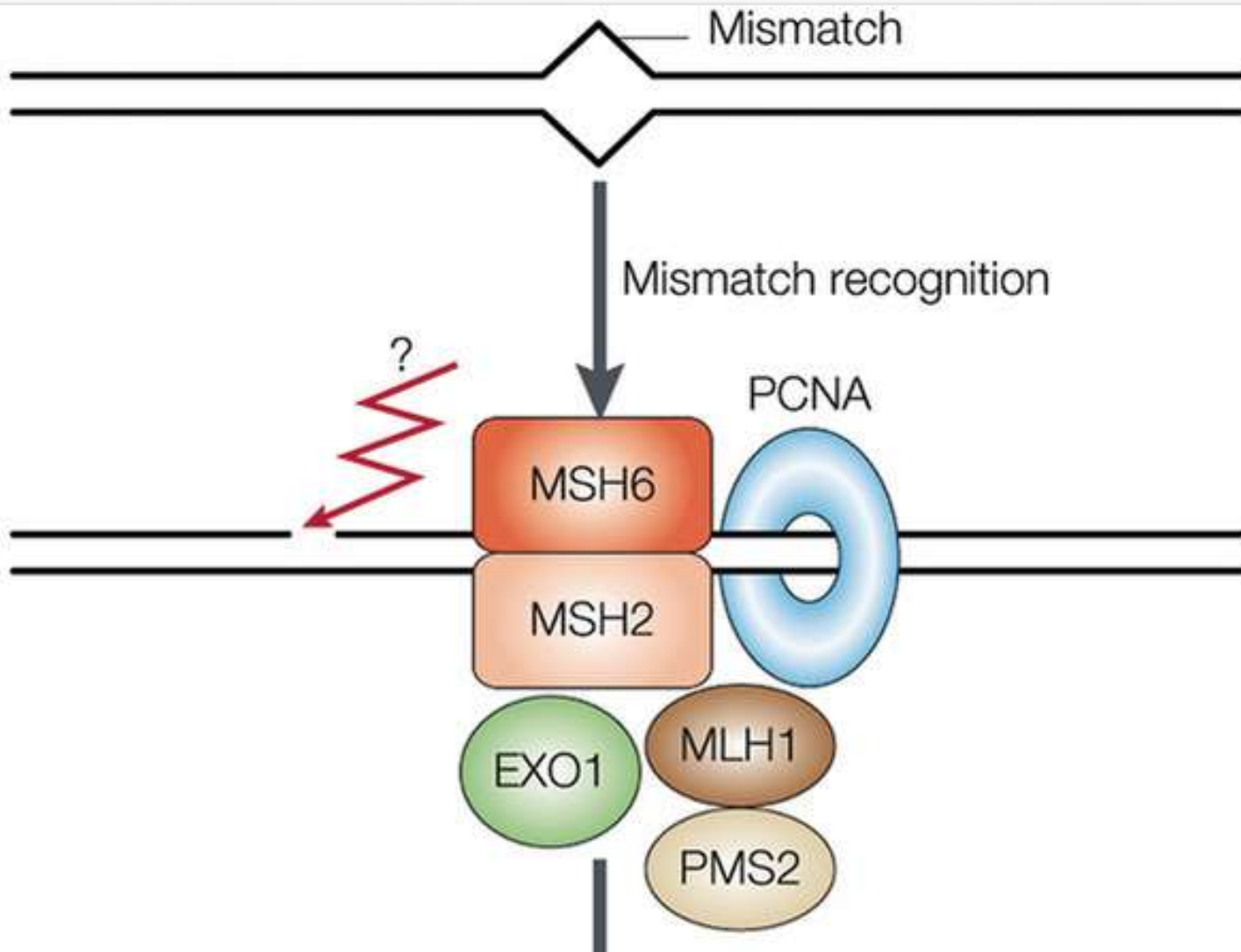
SLIDE DA PROFA. APARECIDA

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
2p21-p16	Colorectal cancer, hereditary nonpolyposis, type 1	120435	<u>AD</u>	3	MSH2	609309

REPARO DE MALPAREAMENTO

(slide da Profa. Aparecida)



Malpareamento - Mismatch

<http://highered.mheducation.com/sites/dl/free/0072835125/126997/animation34.html>

Observar que o filme é para E. coli

O reparo de malpareamento corrige os erros replicativos

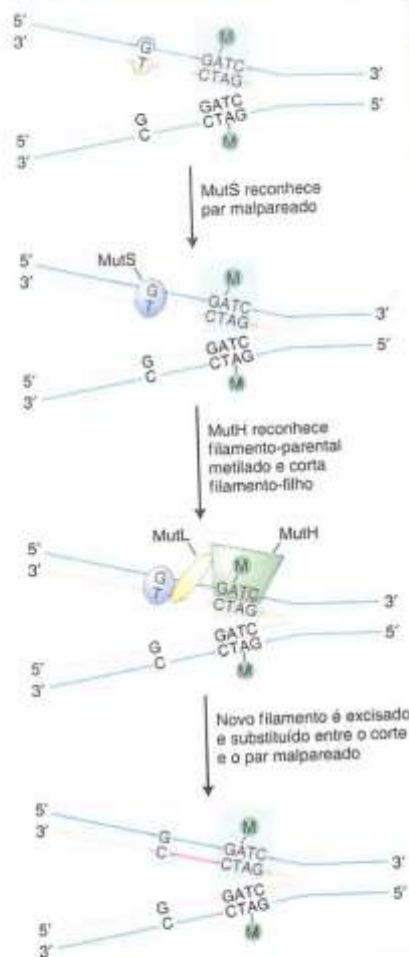


FIGURA 16.23 Modelo em relação ao reparo de malpareamento em *E. coli*. O DNA é metilado (Me) no resíduo A na sequência GATC. A replicação do DNA produz um dúplex hemimetilado que existe até que a metilase consiga modificar o filamento recém-sintetizado. O sistema de reparo de malpareamento realiza quaisquer correções necessárias com base na sequência observada no filamento metilado (modelo original). MutS, MutH e MutL são proteínas.

REPARO DE MALPAREAMENTO

(slide da Profa. Aparecida)

MMR é o principal sistema de reparo e ocorre durante a replicação do DNA



Mutação por perda de função em genes do sistema MMR podem resultar em uma instabilidade global do DNA .



Células com deficiência da maquinaria MMR, a taxa de mutação pode aumentar 1000 vezes

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	trichothiodystrophy	-	+	+	-
Single-strand break (SSB) repair	ataxia oculomotor apraxia 1	-	-	+	-
	spinocerebellar ataxia with axonal neuropathy I	-	-	+	-
Interstrand cross-link repair	Fanconi anemia	+	+	+	+
Double-strand break (DSB) repair (NHEJ)	Lig4 syndrome	+	-	+	+
	severe combined immunodeficiency	-	-	-	+
DNA damage signaling/DSB repair	ataxia telangiectasia	+	-	+	+
	Seckel syndrome	-	-	+	+
	primary microcephaly 1	-	-	+	-
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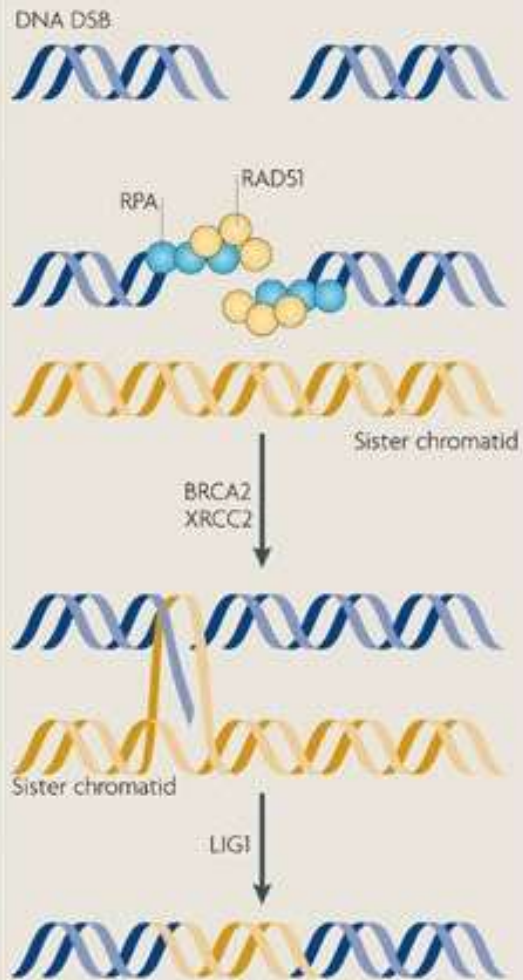
Ataxia-telangectasia

- Protótipo de doença relacionada às alterações de reparo – complexa
- Gene *ATM* (“sensor” de danos)
- Junção de extremidades (pontas) não homólogas
- Padrão de herança AR
- Neurologia. Por quê?
- Alterações dermatológicas
- Alterações oftalmológicas
- Alterações imunológicas
- OMIM

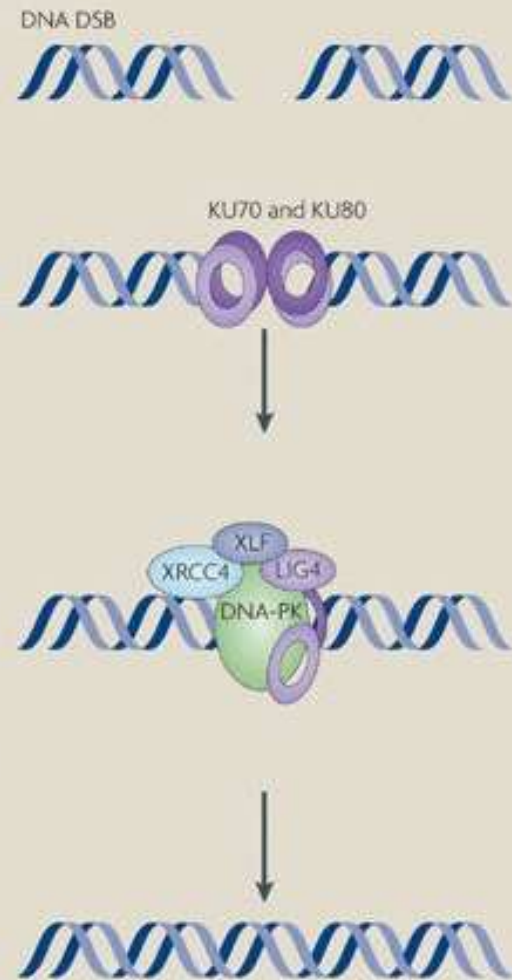


Double strand breaks

a Homologous recombination



b Non-homologous end joining



Repare que há outras ataxias

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Homologous recombination (HR)	Bloom syndrome	+	-	+	+
Telomere maintenance (TM)	dykeratosis congenita	+	+	+	+
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ATAXIA ESPINOCEREBELAR- EPILEPSIA (slide da Profa. Aparecida)

DOENÇAS NEURODEGENERATIVAS

O Locus *hOGG1* apresenta várias isoformas. Algumas codificam enzimas que localizam-se nas mitocôndrias e têm atividade glicosilase para reparar lesões do DNA mitocondrial

REPARO DE EXCISÃO DE BASES NO DNA MITOCHONDRIAL

(slide da Profa. Aparecida)

O DNA mitocondrial está mais sujeito a danos com as espécies reativas de oxigênio comparado ao DNA nuclear



O número de bases oxidadas no DNA mitocondrial é 2-3 vezes maior que no DNA nuclear.



O SNC tem alta demanda energética utilizada principalmente para manter a distribuição iônica através da membrana e para função sináptica

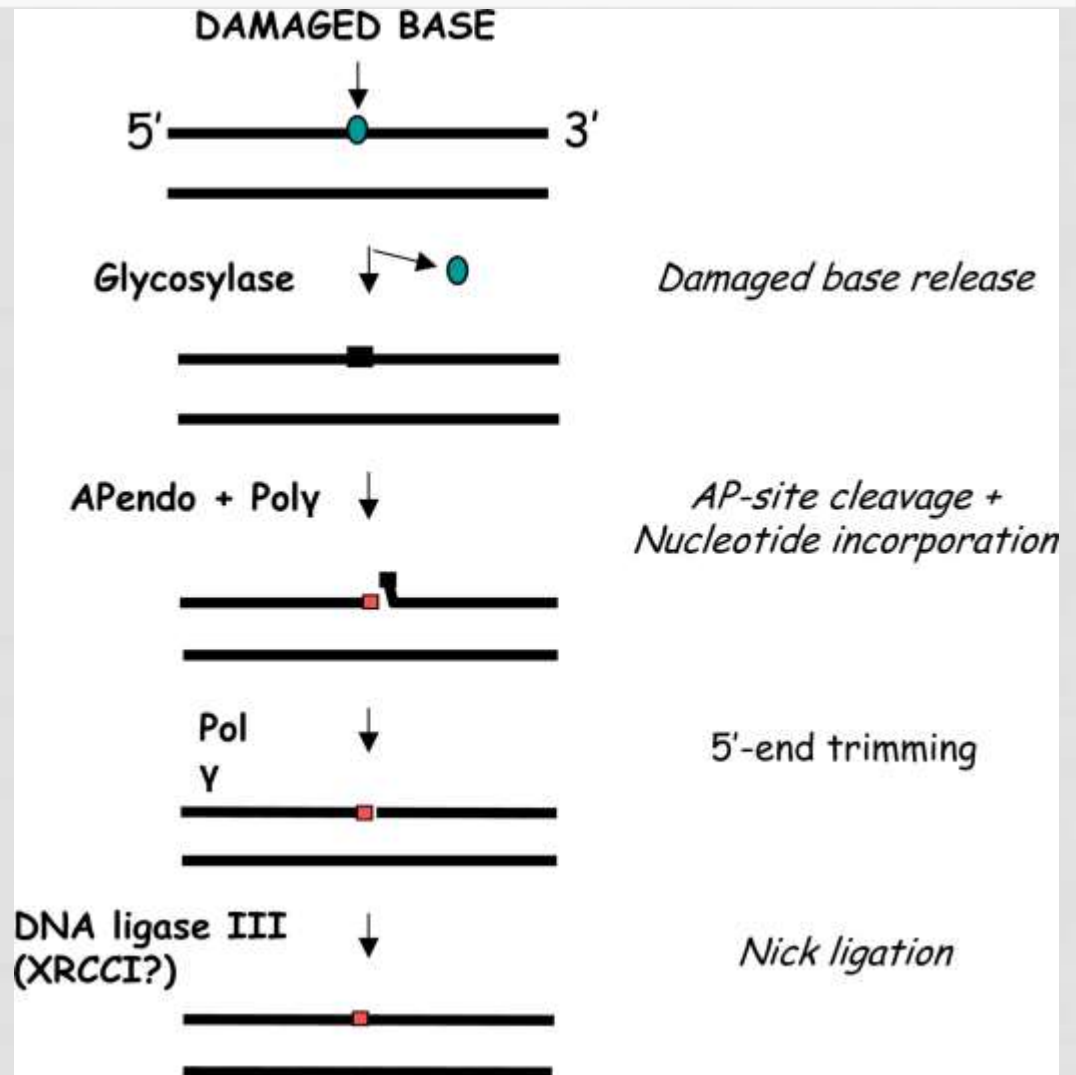


Perda da integridade mitocondrial está associada com neurodegeneração

REPARO DE EXCISÃO DE BASES NO DNA MITOCHONDRIAL

(slide da Profa. Aparecida)

DNA GLICOSILASE



MECANISMOS DE REPARO DO DNA MITOCHONDRIAL

(slide da Profa. Aparecida)

Mammalian DNA Repair Pathways

PATHWAY	SUBPATHWAYS	Nuclear	Mito
BER/SSBR	Long patch	Y	N
	Short patch	Y	Y
NER	General genome	Y	N
	Gene-specific	Y	N
	Transcription associated	Y	N
MMR		Y	Y?
Recombination	HR	Y	?
	NHEJ	Y	Y
Direct damage reversal		Y	Y