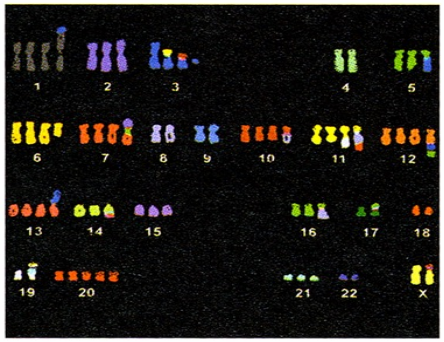
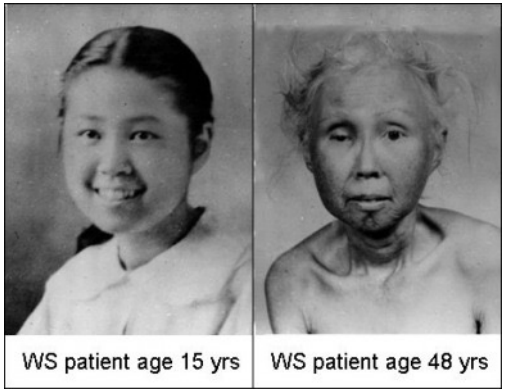
IL DANNO AL DNA

Instabilità genetica e danno al DNA

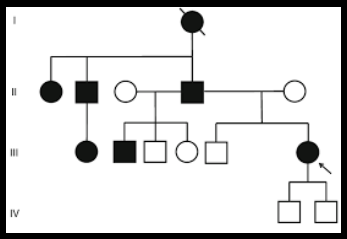
Instabilità genetica



Cancro



Invecchiamento



Ataxia telangiectasia	ATM
Seckel syndrome	ATR
AT-like disease	MRE11
Bloom syndrome	BLM
Coats Plus	CST
Xeroderma pigmentoso	NER

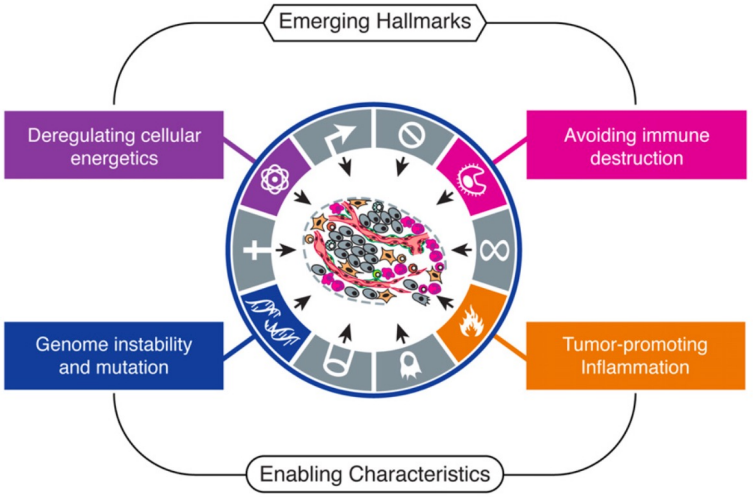
Malattie genetiche

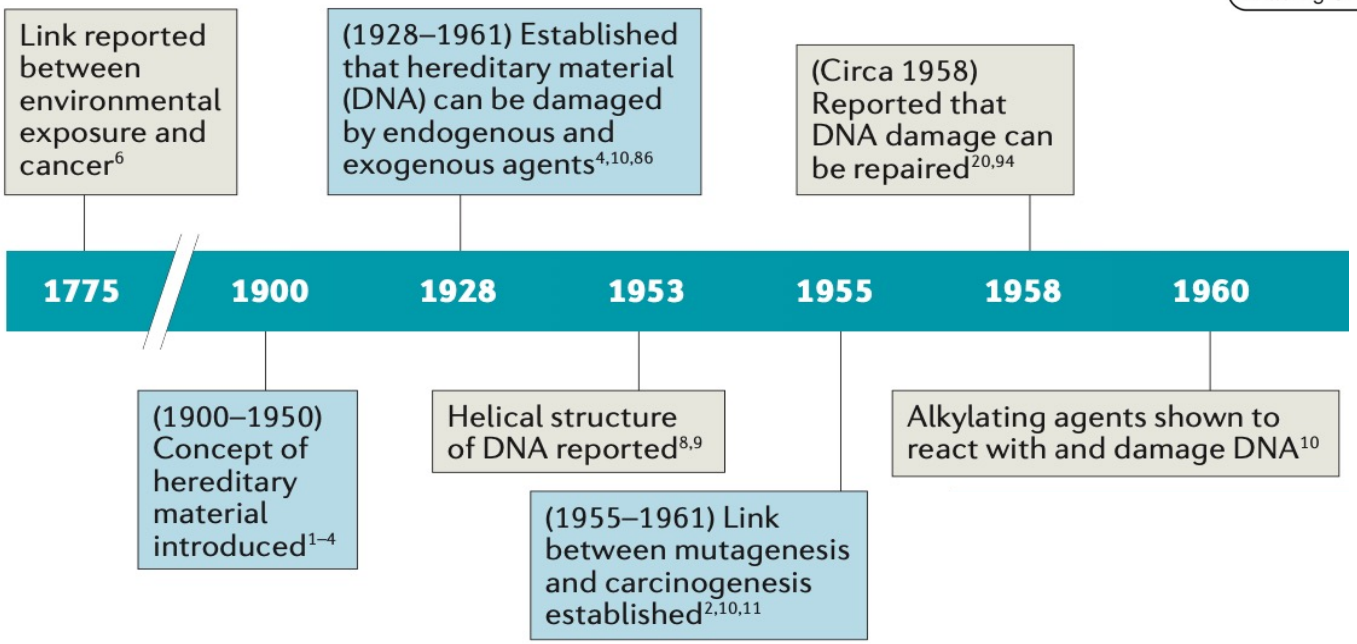
Instabilità genetica e danno al DNA

TIMELINE

DNA repair, genome stability and cancer: a historical perspective

Penny A. Jeggo, Laurence H. Pearl and Antony M. Carr

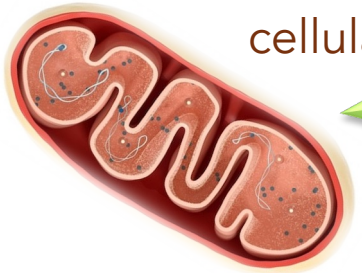




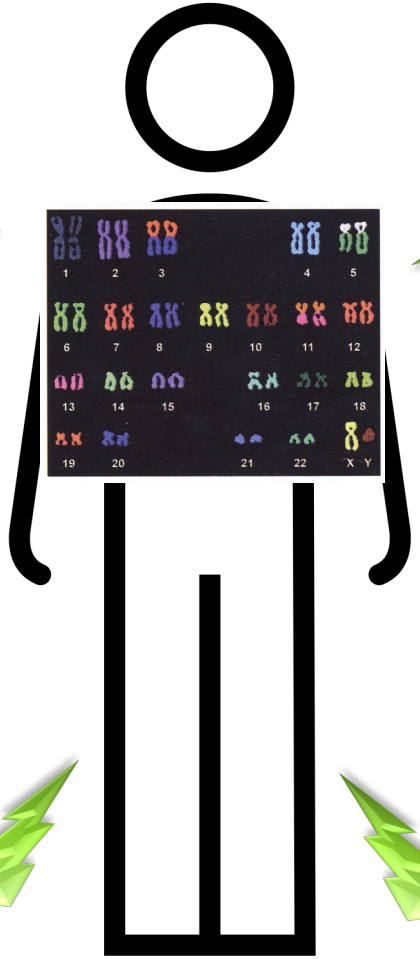
Jeggo et al., 2016; Hanahan & Weinberg, 2011

Danni al DNA

Prodotti del Metabolismo cellulare



Errori durante la replicazione

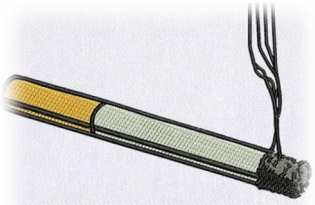


60.000 lesioni al DNA in ogni cellula in un giorno

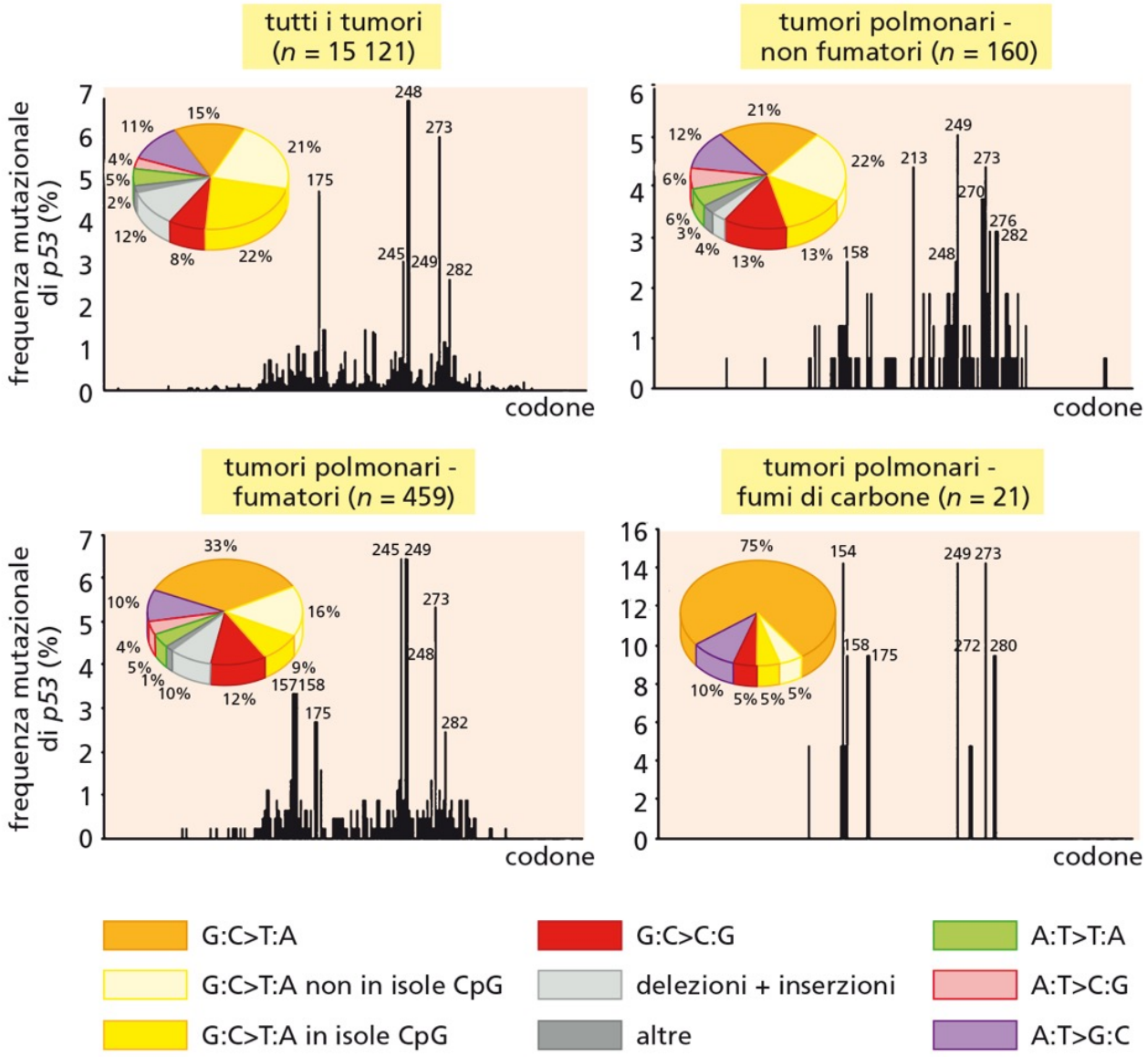
Raggi UV

Radiazioni ionizzanti

Esposizione a sostanze chimiche



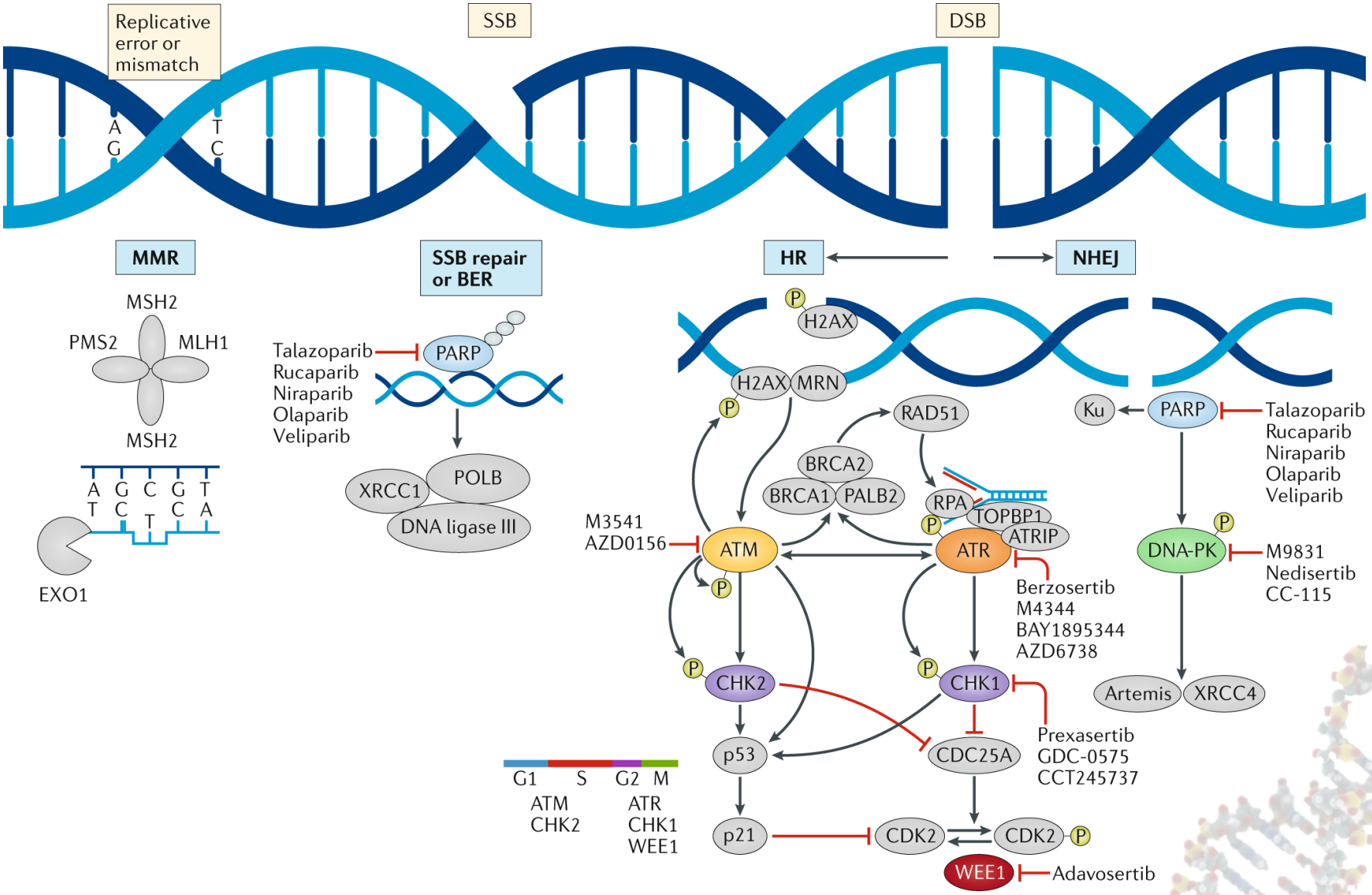
Danni al DNA e mutazioni



Weinberg, La biologia del cancro

Danni al DNA

Riparazione del DNA



Instabilità genetica e danno al DNA

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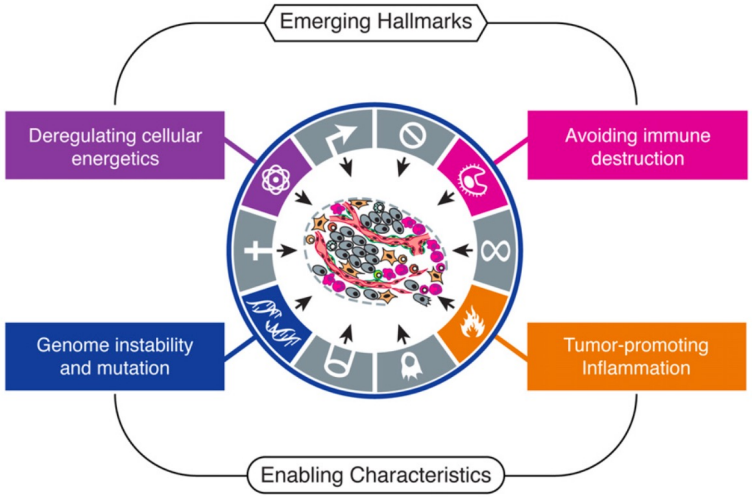
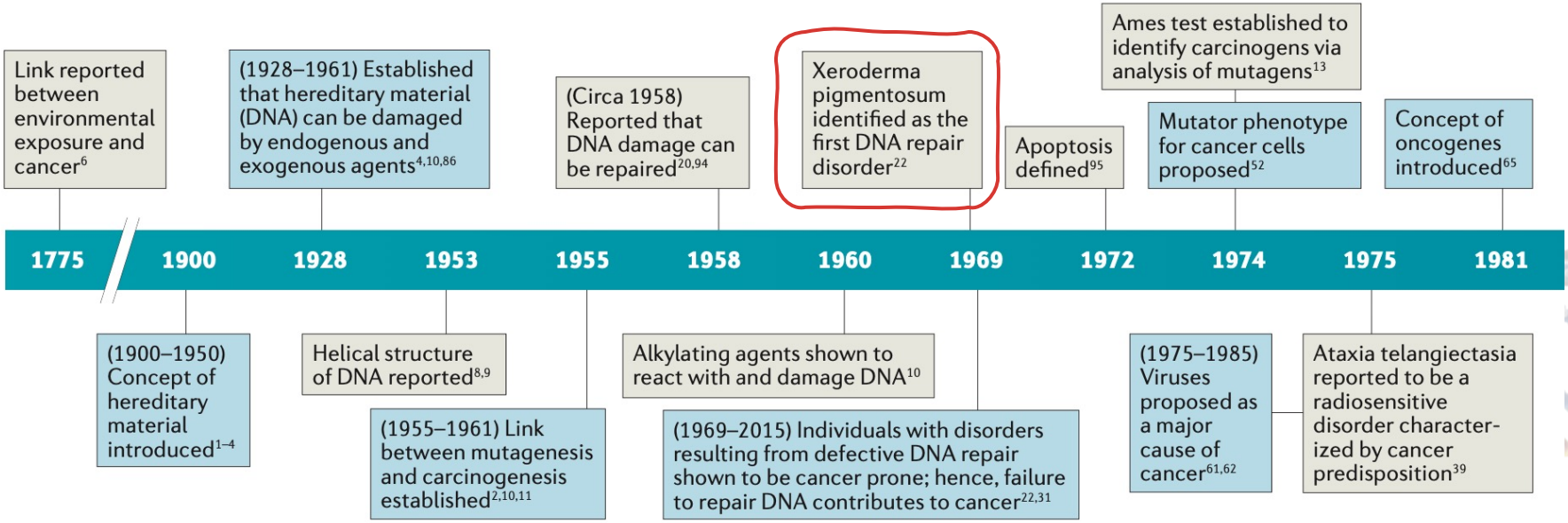




Jeggo et al., 2016; Hanahan & Weinberg, 2011

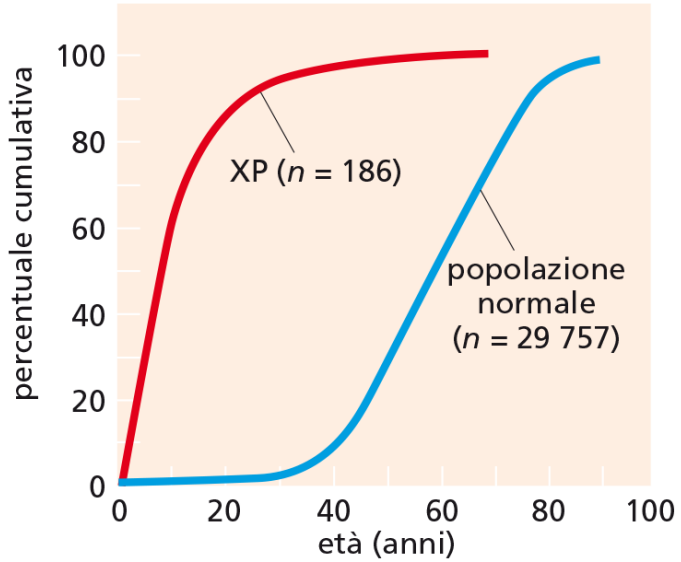
XP e i difetti di riparazione

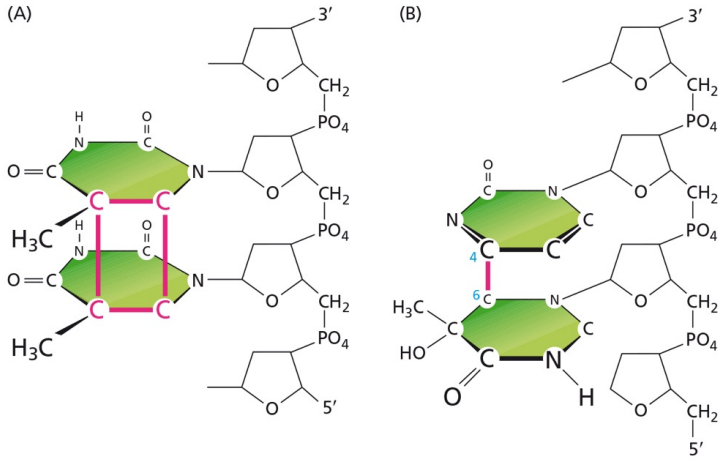
*XERODERMA PIGMENTOSUM: A HUMAN DISEASE IN WHICH AN INITIAL STAGE OF DNA REPAIR IS DEFECTIVE**

By J. E. Cleaver

Cells from patients with XP were defective in the ability to repair DNA damage caused by ultraviolet (UV) light

Comparsa tumori cutanei:

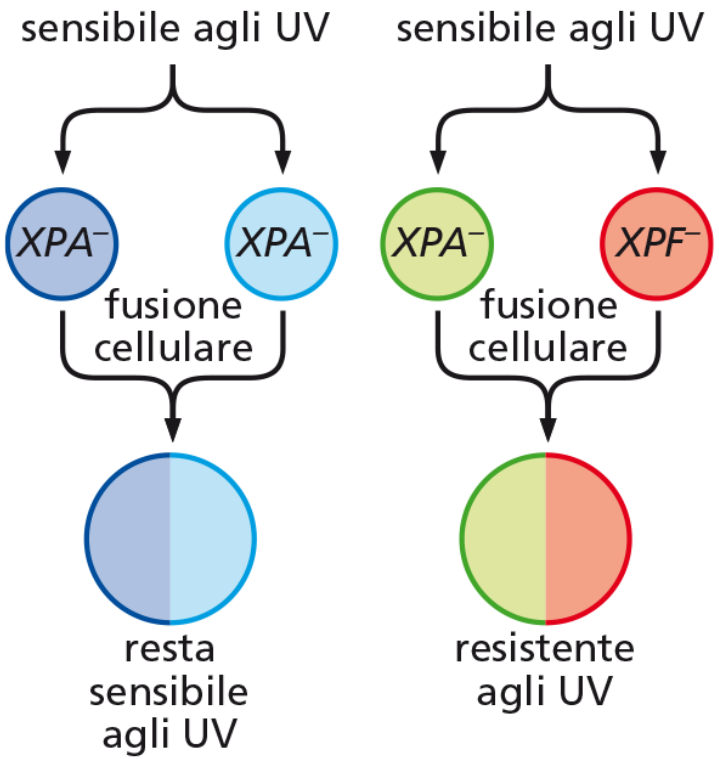


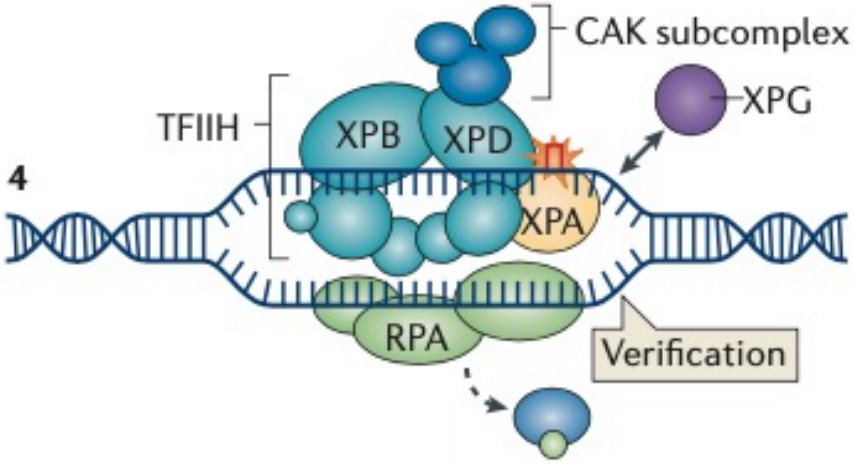


Cleaver, 1969, Weinberg, La biologia del cancro

XP e i difetti di riparazione

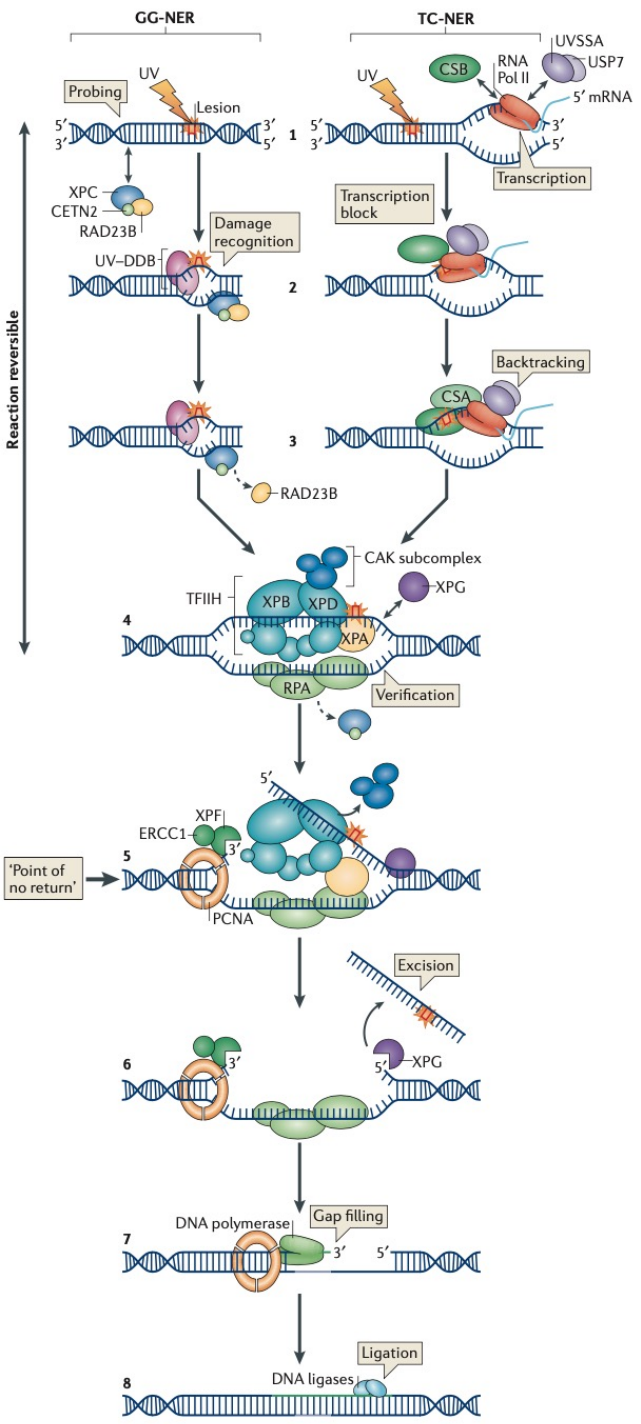
Identificazione geni XP per complementazione: 8 gruppi





Cleaver, 1969, Weinberg, La biologia del cancro

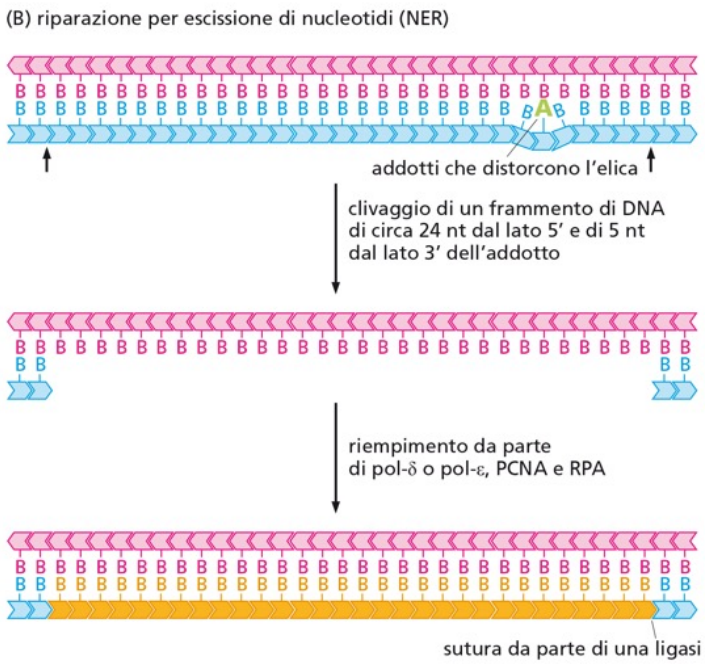
XP e i difetti di riparazione



DNA DAMAGE

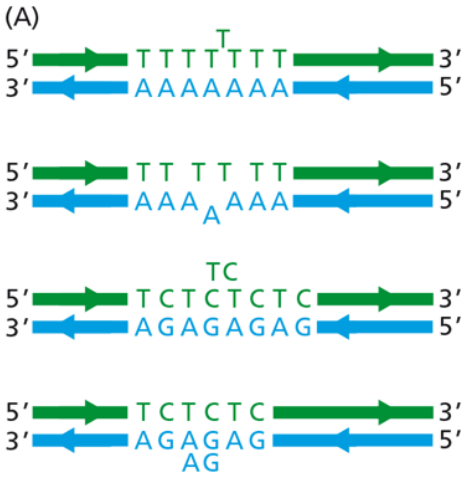
Understanding nucleotide excision repair and its roles in cancer and ageing

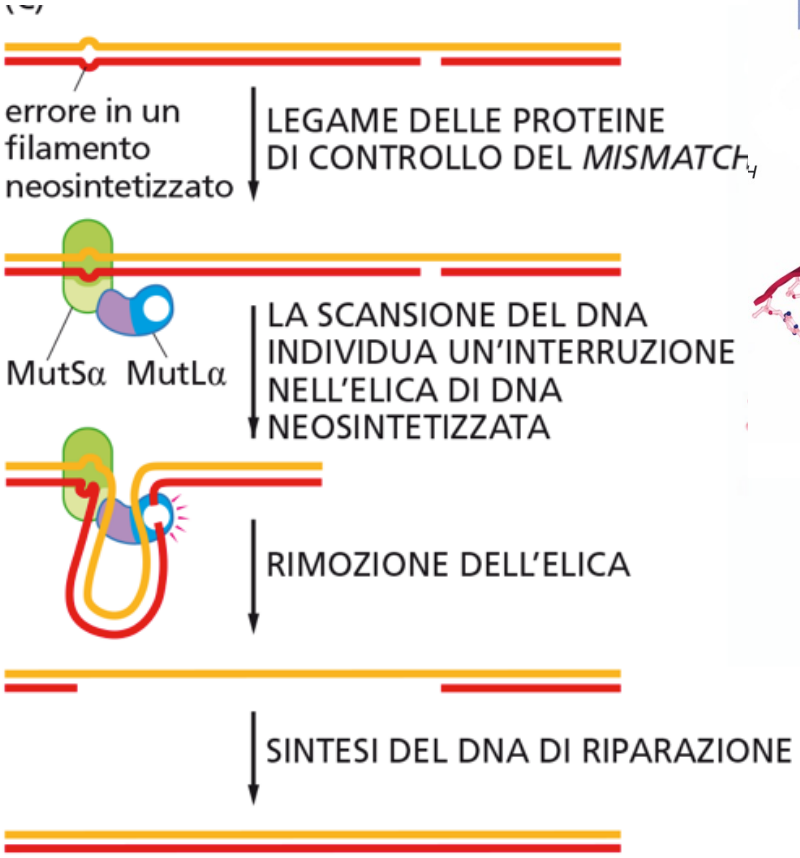
Jurgen A. Marteijn, Hannes Lans*, Wim Vermeulen, Jan H. J. Hoeijmakers*

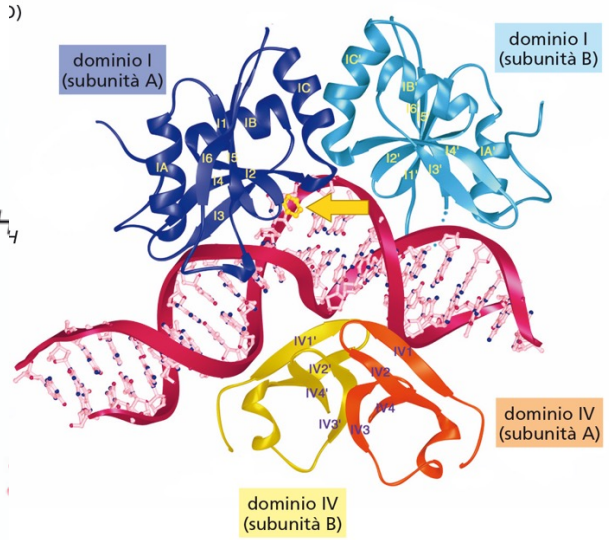


Marteijn et al., 2019, Weinberg, La biologia del cancro

Sindrome di Lynch (HNPCC)







Peggo et al., 2016; Weinberg, La biologia del cancro

Sindrome di Lynch (HNPCC)

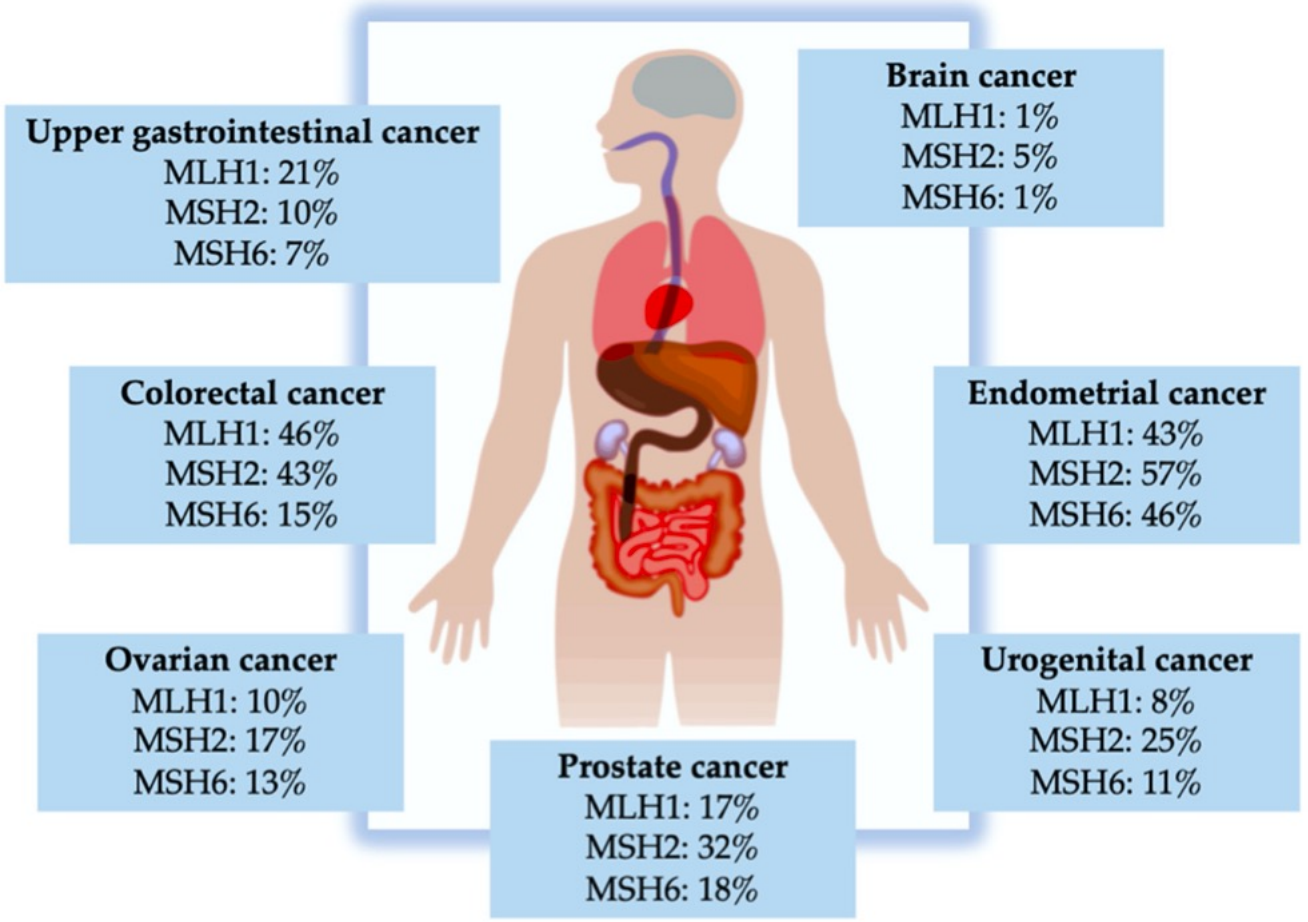


Figure 3. Incidence rate of Lynch syndrome (LS)-associated cancers depending on the involved mismatch repair (MMR) gene mutation up to the age of 75 years [28].

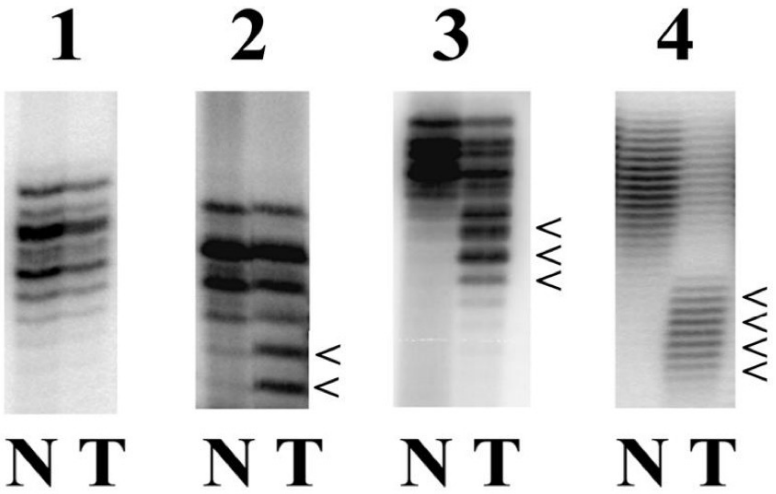
Lindner et al., 2021; Weinberg, La biologia del cancro

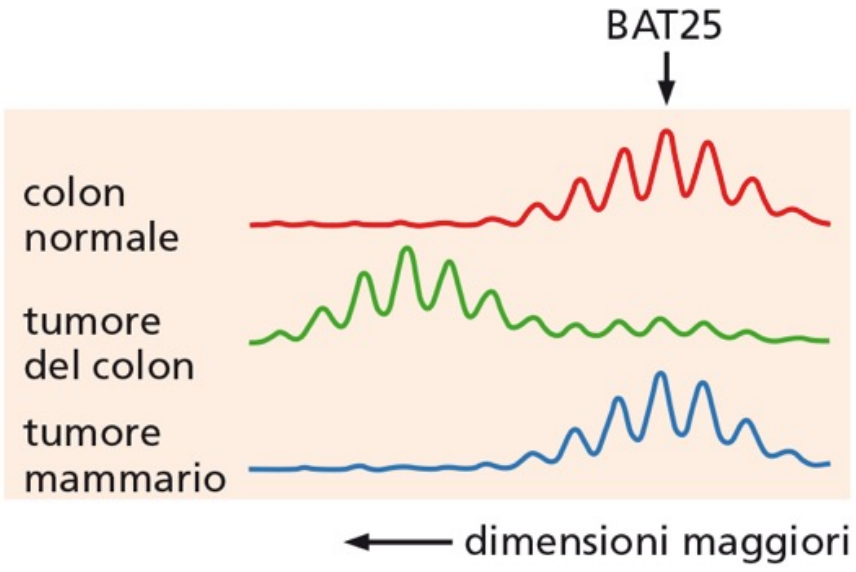
Sindrome di Lynch (HNPCC)

DNA microsatellitare

...AAAAAAAAAAAAAAAAAAAA.. (ripetizione mononucleotidiche)

...CACACACACACACACACACA... (ripetizione dinucleotidiche)

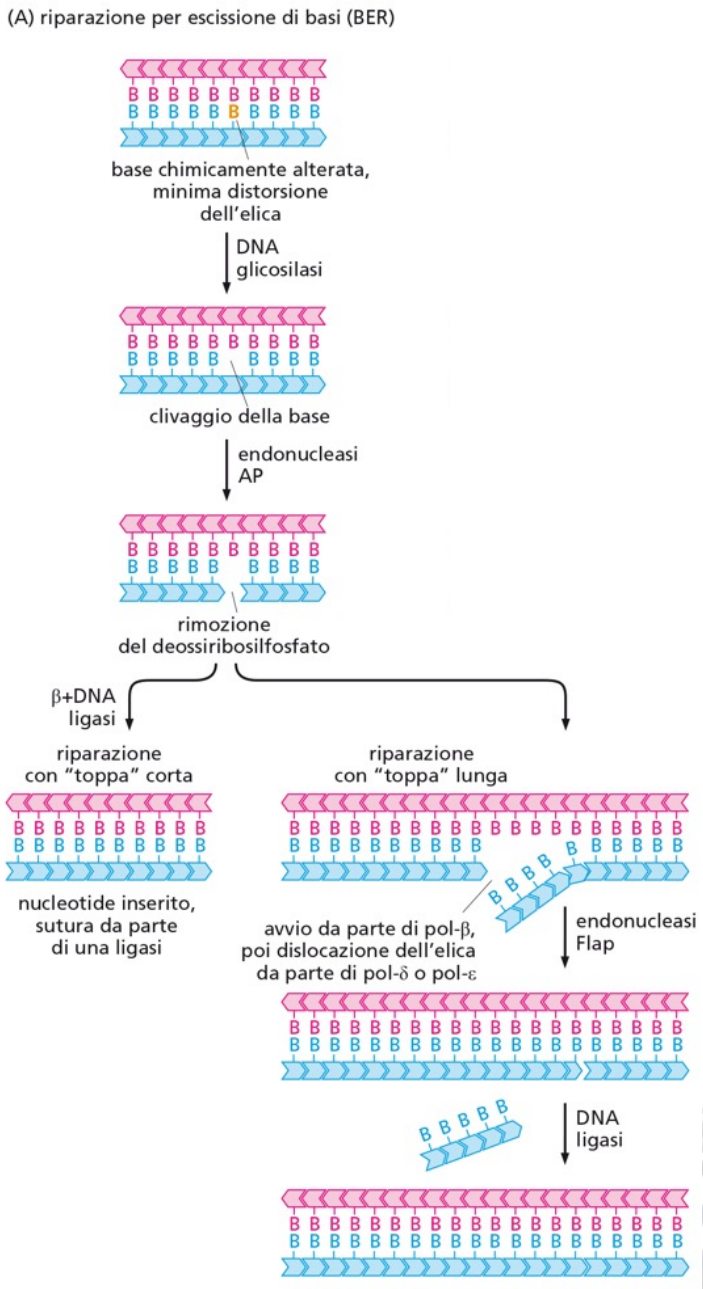




Lindner et al., 2021; Weinberg, La biologia del cancro

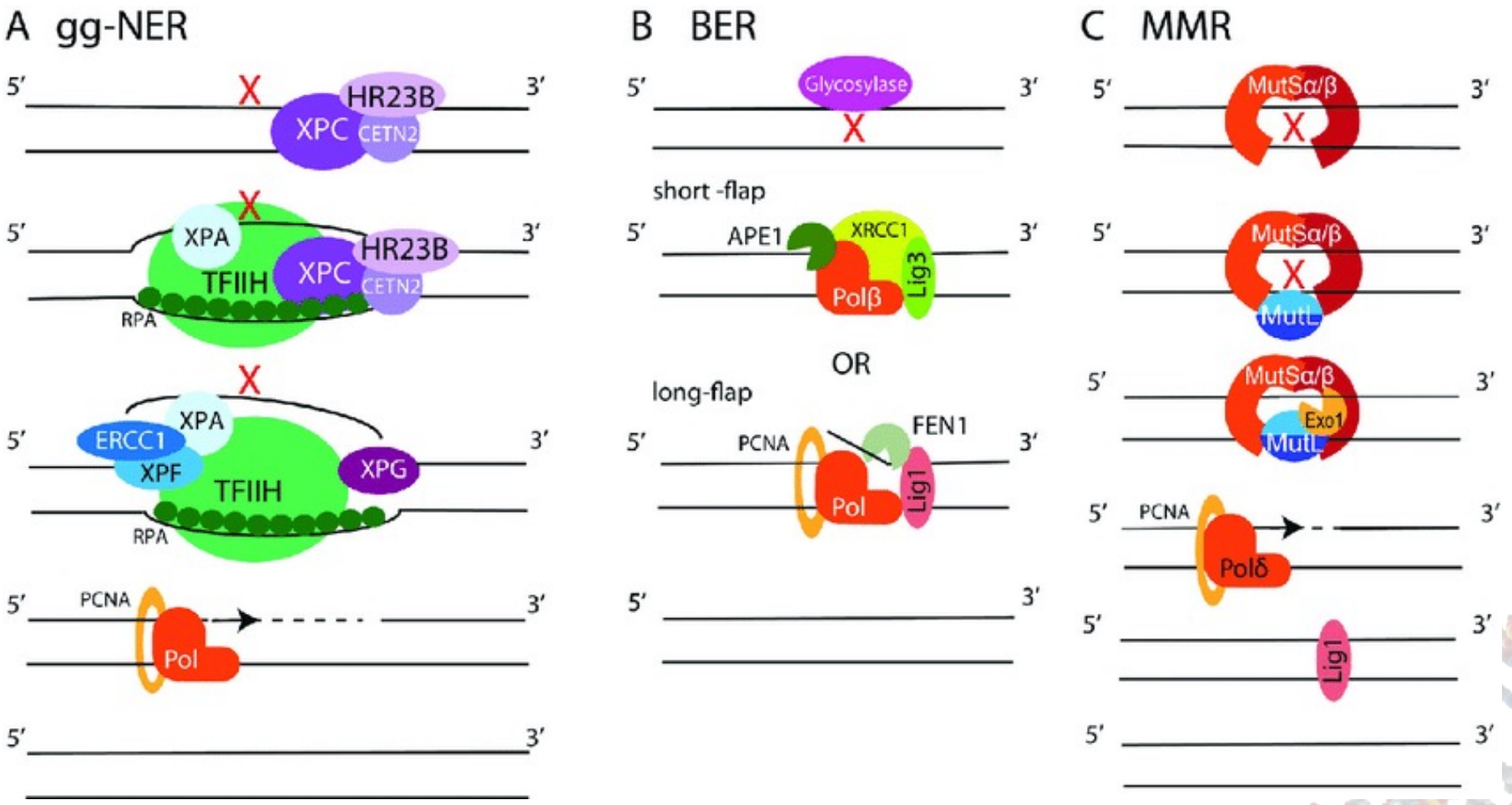
Base Excision Repair (BER)

- Enzimi dealchilanti
- DNA polimerasi proof reading
- DNA polimerasi translesione



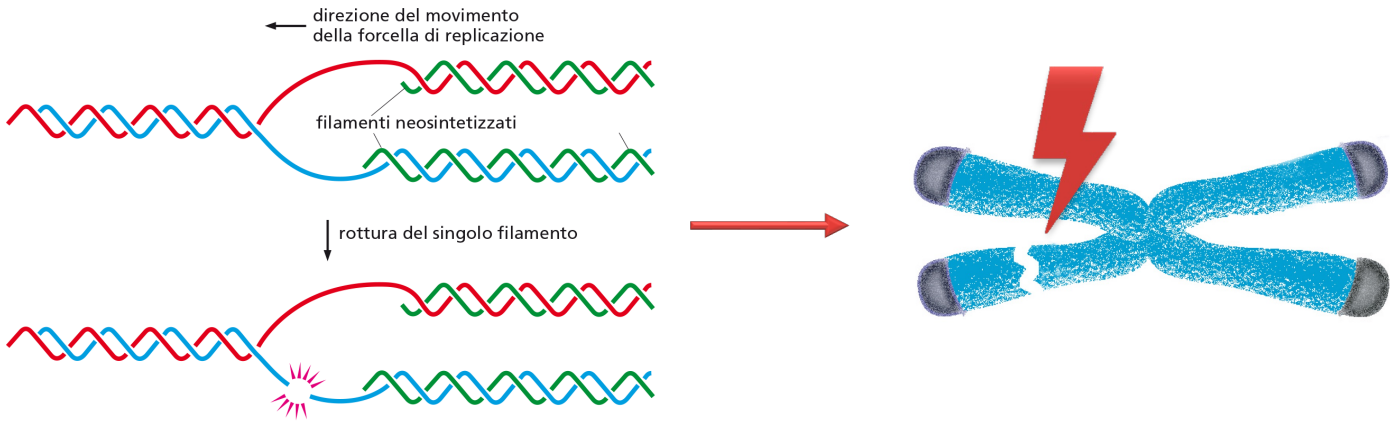
Cleaver, 1969

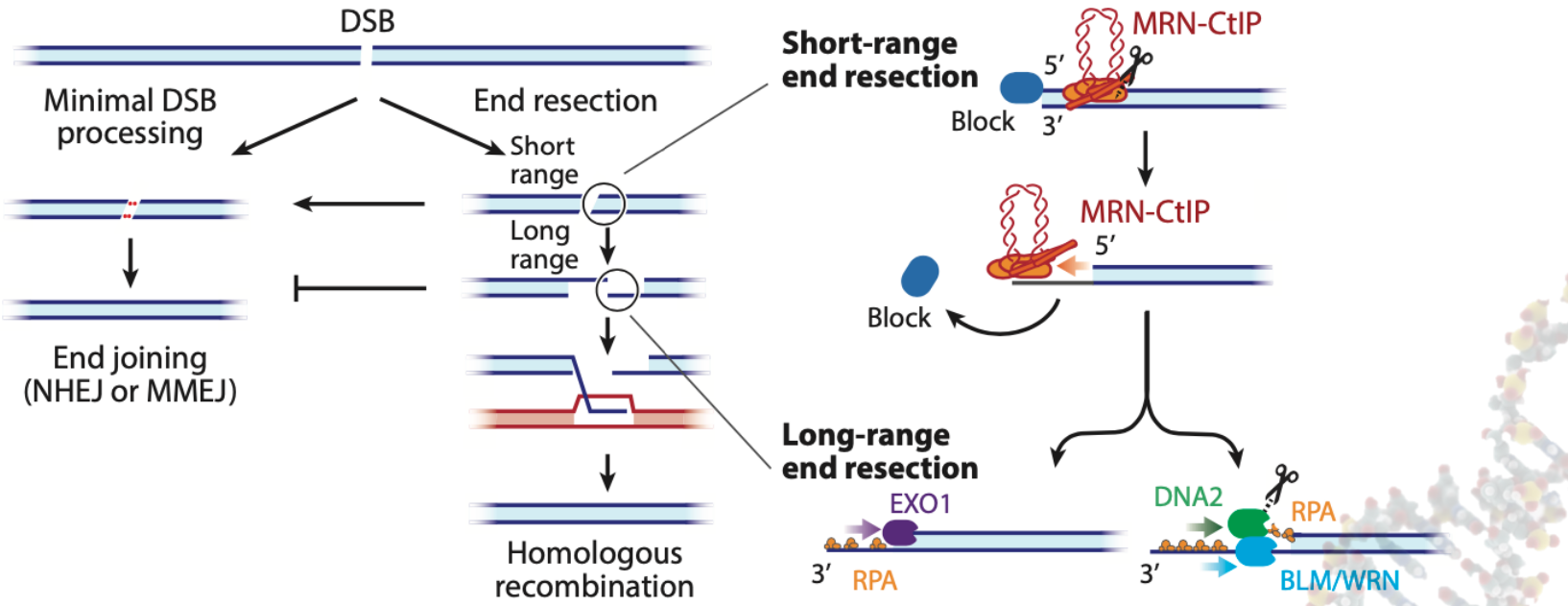
Base Excision Repair (BER)



Cleaver, 1969

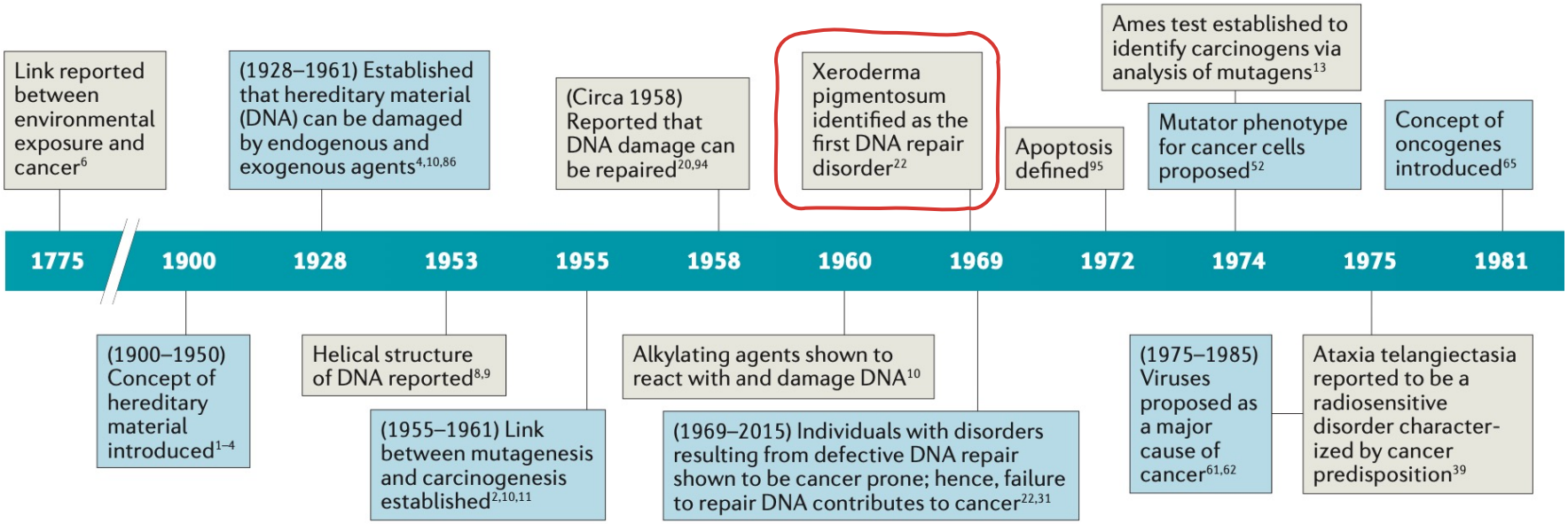
Rottura del doppio filamento e sua riparazione





Symington & Cejka, 2019

Instabilità genetica e danno al DNA



DANNO non riparato → Mutazione in oncogene o oncosoppressore → → CANCRO

Instabilità genetica è causa o conseguenza di carcinogenesi? Quando avviene nello sviluppo del cancro?

Jeggo et al., 2016;

Difetti di riparazione e tumori

TABELLA 12.1

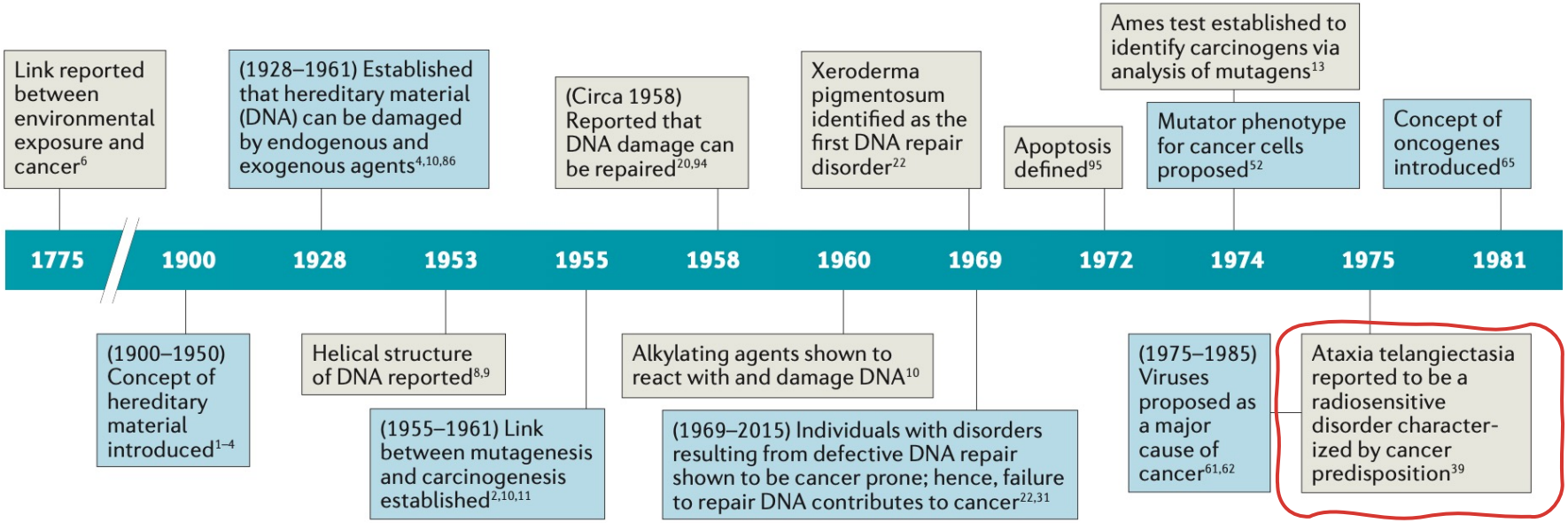
Sindromi tumorali umane eredo-familiari dovute ad alterazioni della riparazione del DNA presenti nella linea germinale

Nome della sindrome	Nome del gene	Fenotipo tumorale	Enzima o processo alterato
HNPCC/Lynch	(4–5 geni)[a]	poliposi del colon	enzimi di riparazione del *mismatch*
XP[b]	(8 geni)[b]	tumori cutanei indotti da UV	riparazione per escissione di nucleotidi
Atassia-teleangectasia (AT)[c]	*ATM*	leucemia, linfoma	risposta a rotture del DNA a doppia elica
Malattia a tipo AT[c]	*MRE11*	cancro del polmone e della mammella	riparazione del DNA a doppia elica mediante NHEJ
Cancro familiare di mammella e ovaio	*BRCA1*, *BRCA2*[d], *BACH1*, *RAD51C*	carcinomi della mammella, dell'ovaio e della prostata	riparazione per omologia di rotture della doppia elica
Werner	*WRN*	sarcomi, altri tumori	esonucleasi e DNA elicasi[e], replicazione
Bloom	*BLM*	leucemie, linfomi, tumori solidi	DNA elicasi, replicazione
Anemia di Fanconi	(13 geni)[f]	AML, carcinomi diversi	riparazione dei legami crociati del DNA e delle rotture a doppia elica
Rottura di Nijmegen[g]	*NBS*	per lo più linfomi	processazione delle rotture a doppia elica del DNA, NHEJ
Li-Fraumeni	*TP53*	tumori multipli	proteina di allarme del danno al DNA
Li-Fraumeni	*CHK2*	carcinomi del colon e della mammella	chinasi che segnala un danno al DNA
Rothmund-Thomson	*RECQL4*	osteosarcoma	DNA elicasi
Adenomatosi familiare	*MYH*	adenomi del colon	riparazione per escissione di basi
Cancro familiare della mammella	*PALB2*	cancro mammario	riparazione del DNA a doppia elica da HR

...alleli mutanti. Due geni MMR (*MSH2* e *MLH1*) sono di solito coinvolti nell'NPCC; due al-

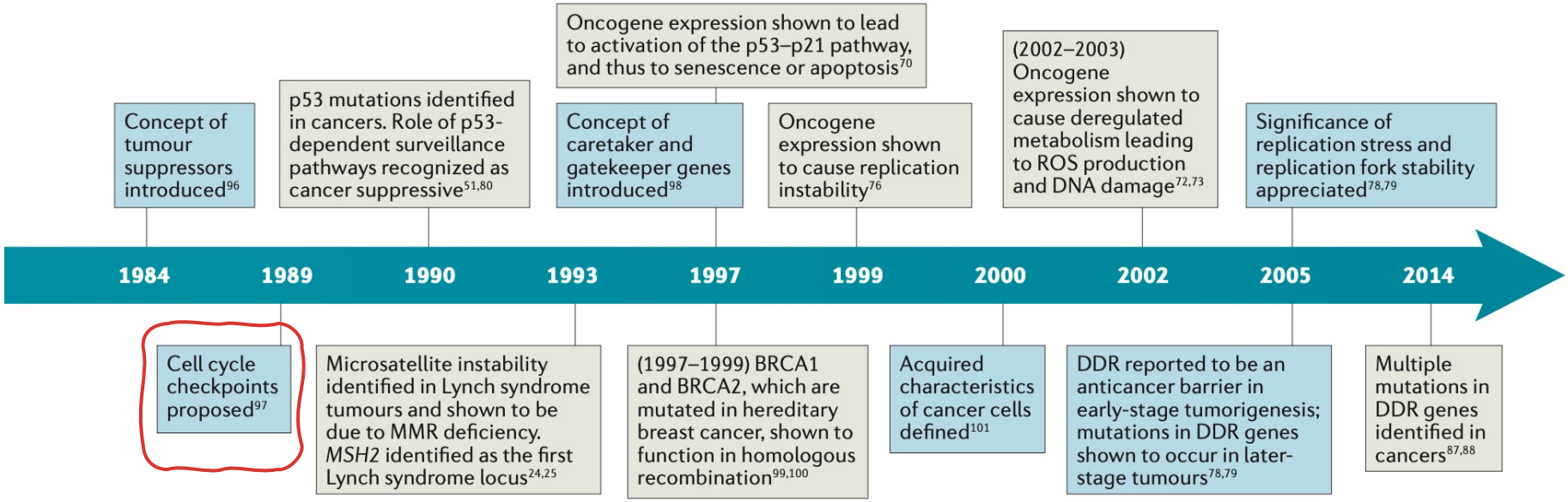
Cleaver, 1969

Instabilità genetica e danno al DNA



Jeggo et al., 2016;

Instabilità genetica e danno al DNA

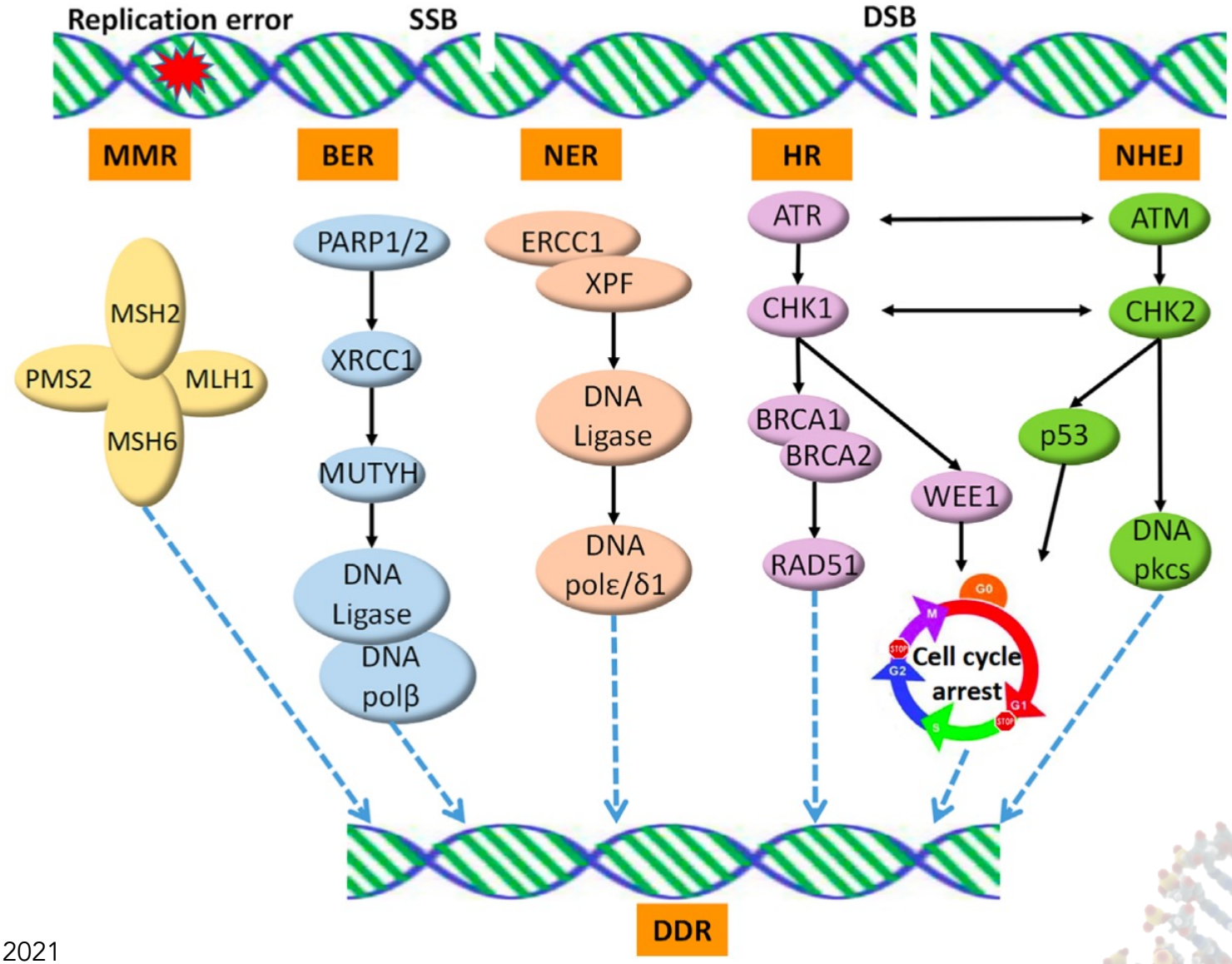


Checkpoints: Controls That Ensure the Order of Cell Cycle Events

LELAND H. HARTWELL AND TED A. WEINERT*

Jeggo et al., 2016; Hanahan & Weinberg, 2011

Checkpoint e riparazione in risposta a danni la DNA



Sun et al., 2021