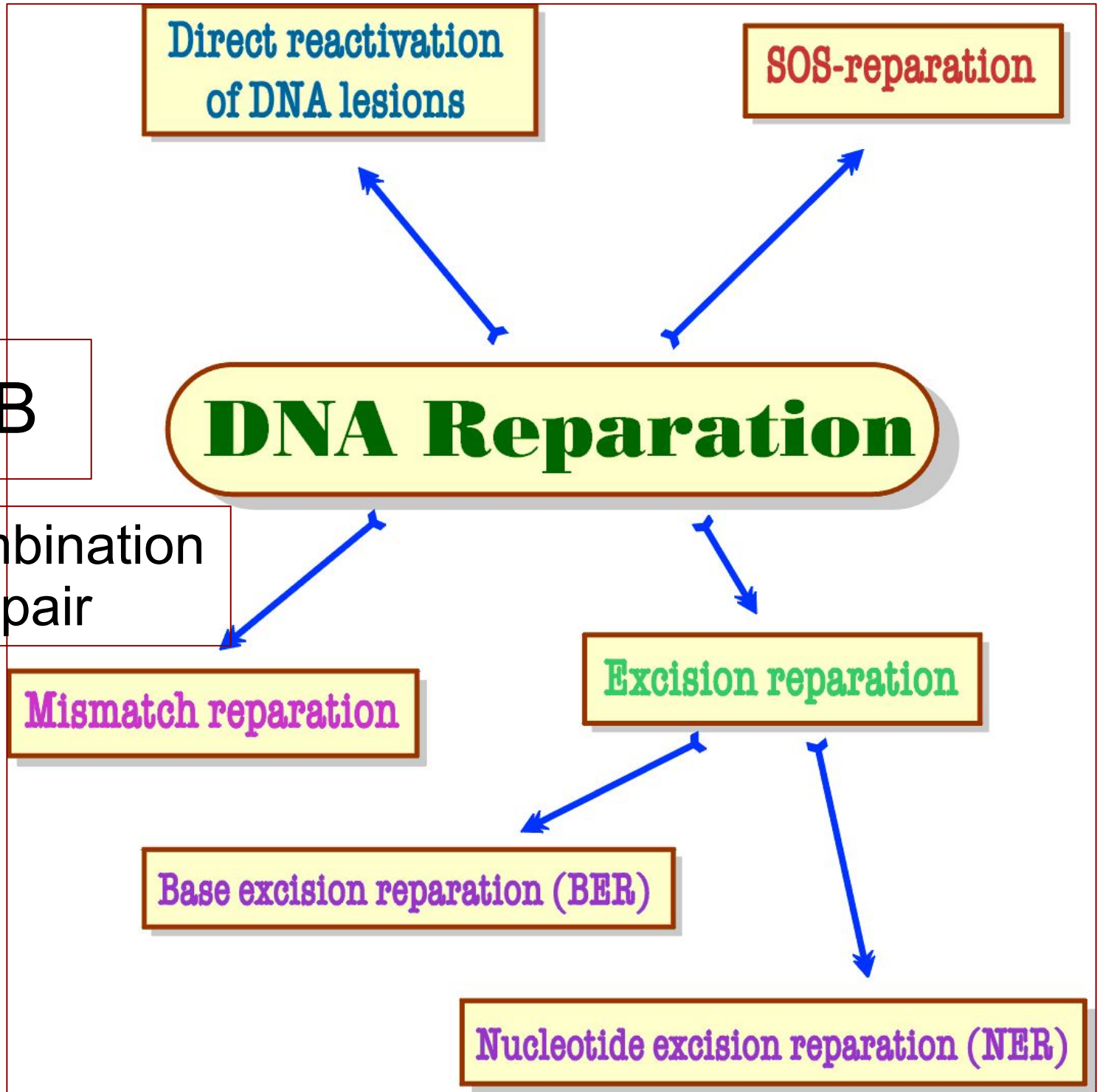
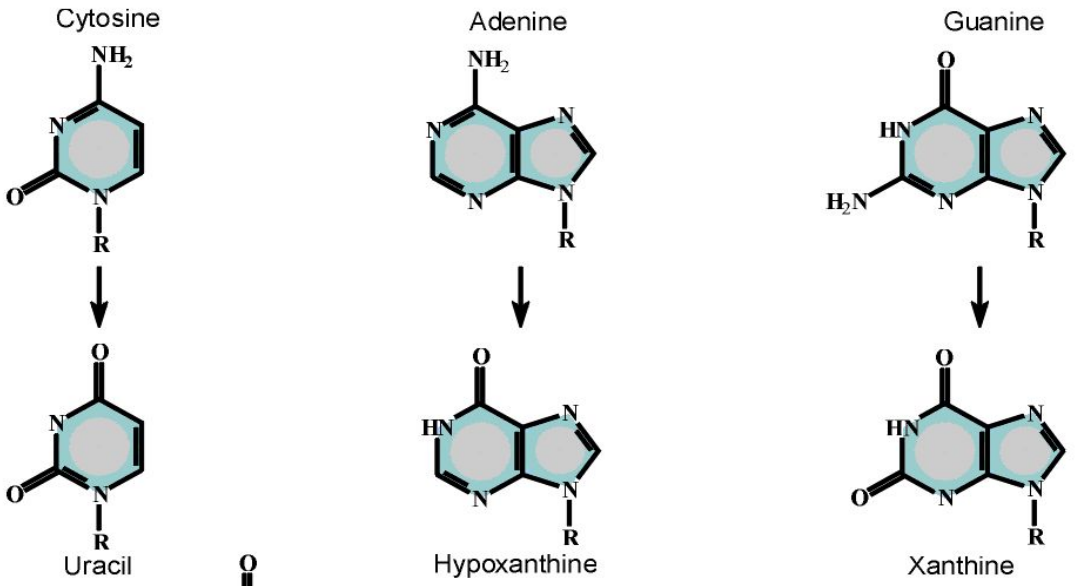


DSB

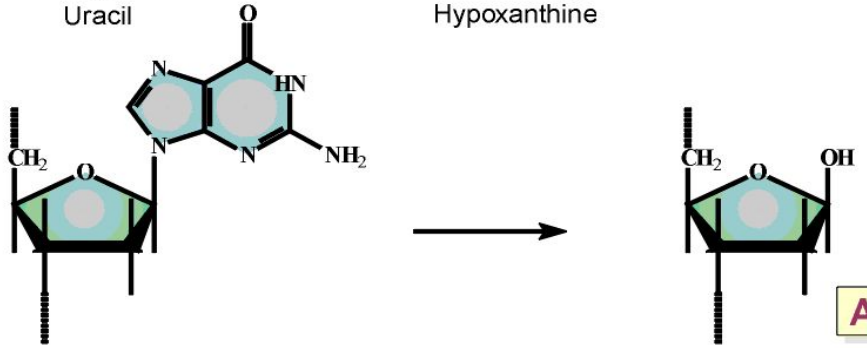
Recombination repair

Typical base lesions

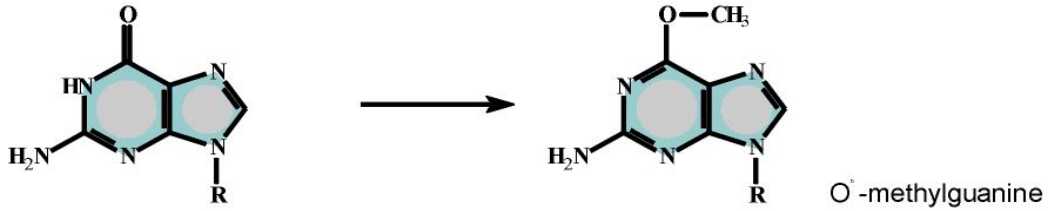
1.



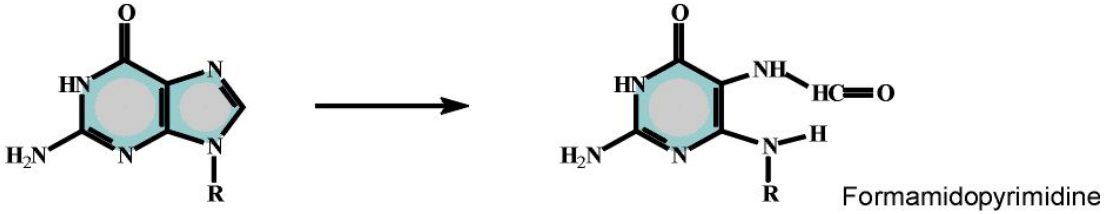
2.

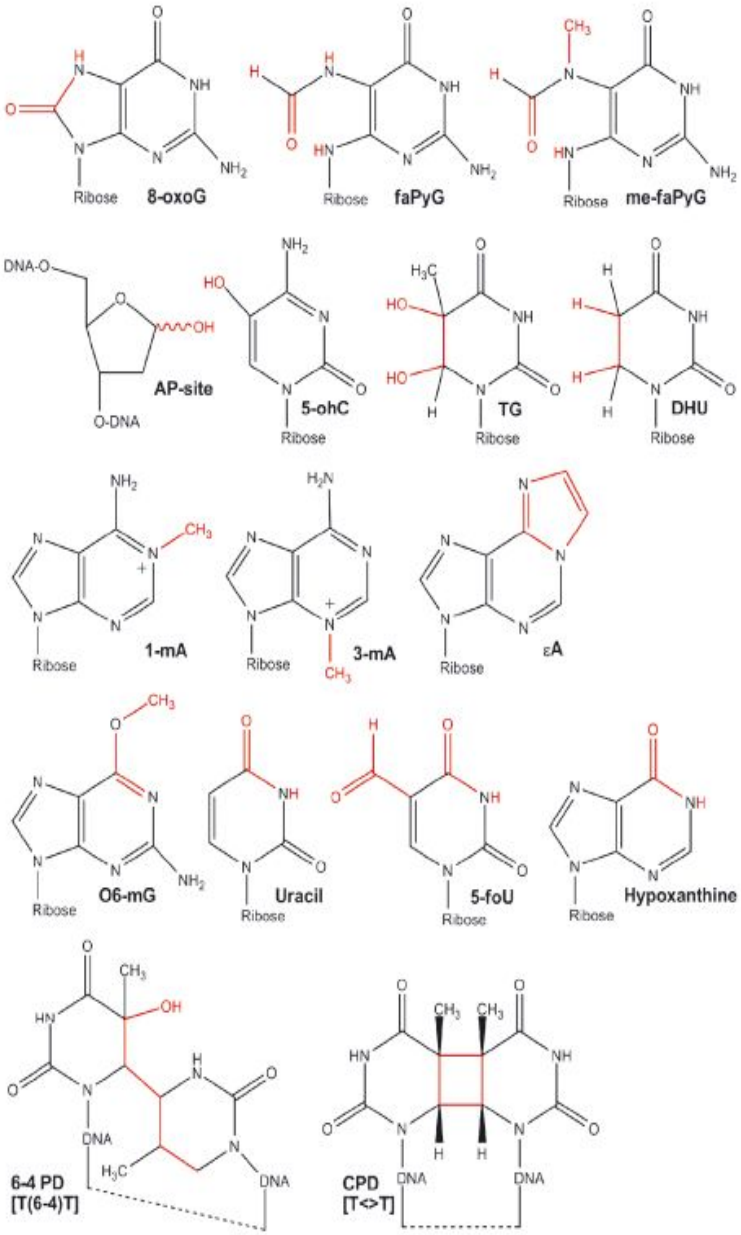


3.



4.

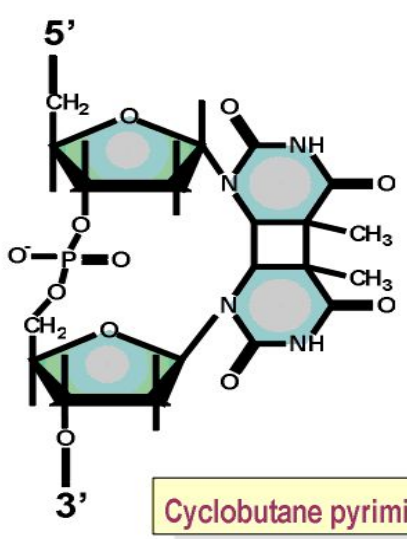




Damaging agent	Prototypical lesions	Major repair mechanism	Prototypical repair enzymes (*E. coli*/human)
Alkylating agents	O6-mG	DR	Transferases: Ogt/Agt
	1-mA	DR	Oxidoreductases: AlkB/Abh2
	3-mA, 3-mG, 7-mA, 7-mG	BER	Glycosylases: AlkA/Aag
Hydrolysis	Abasic sites	BER	Endonucleases: EndoIV/Ape1
	Deamination (forming uracil)	BER	Glycosylases: Ung
	Deamination (forming hypoxanthine)	NIR	Endonucleases: EndoV
ROS	8-oxoG, faPyA/G, TG, 5-ohC, DHU, DHT	BER	Glycoasylases: Fpg, Nth/Ogg1, Nth1
	DHU, DHT, 5-ohC	NIR	Endonucleases: EndoIV/Ape1
Replication errors	(a) Base mismatches	MMR	Mismatch proteins:
	(b) Insertion/deletion loops		MutS, MutL, MutH/MutSα/β, MutLα
UV radiation	Bulky adducts	NER	XPA–XPF+others
	CPDs, 6-4 PDs	DR	Photolyases: CPD and (6-4) photolyases

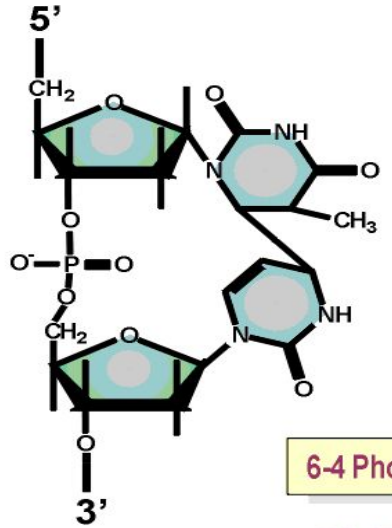
BER, base excision repair; DR, direct reversal; MMR, mismatch repair; NER, nucleotide excision repair; NIR, nucleotide incision repair; ROS, reactive oxygen species.

5.



T T

T C

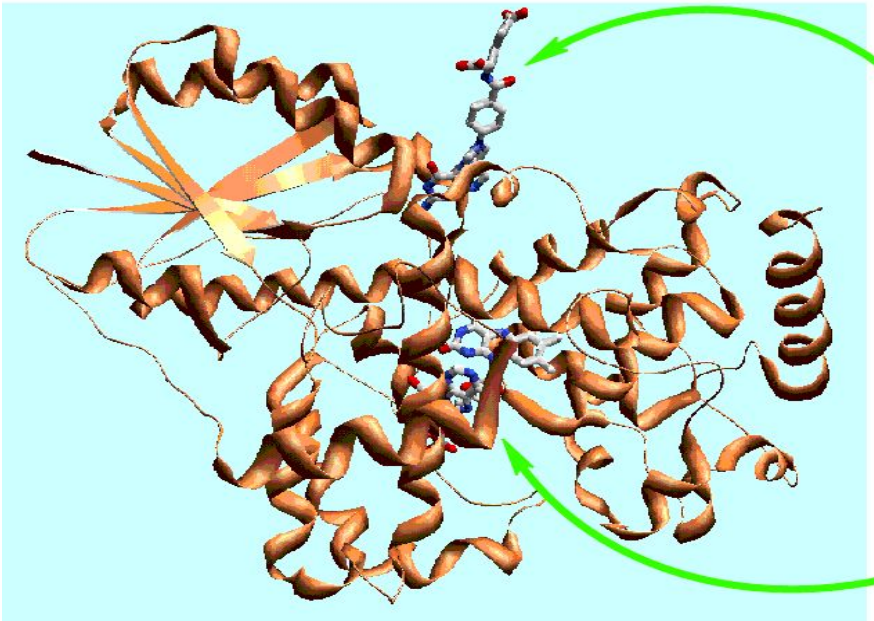


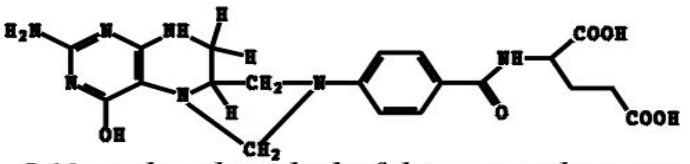
Cyclobutane pyrimidine dimers

Any pyrimidine pair

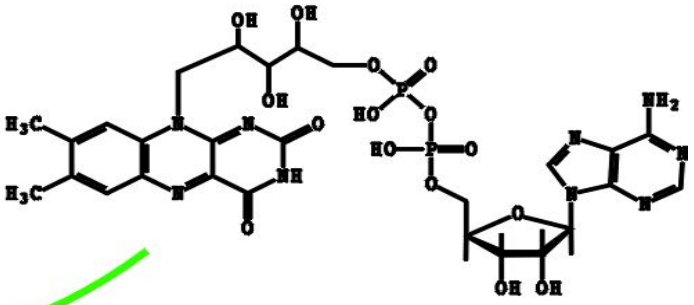
6-4 Photoproducts

5'-T-C-3'
5'-T-T-3'
5'-C-C-3'

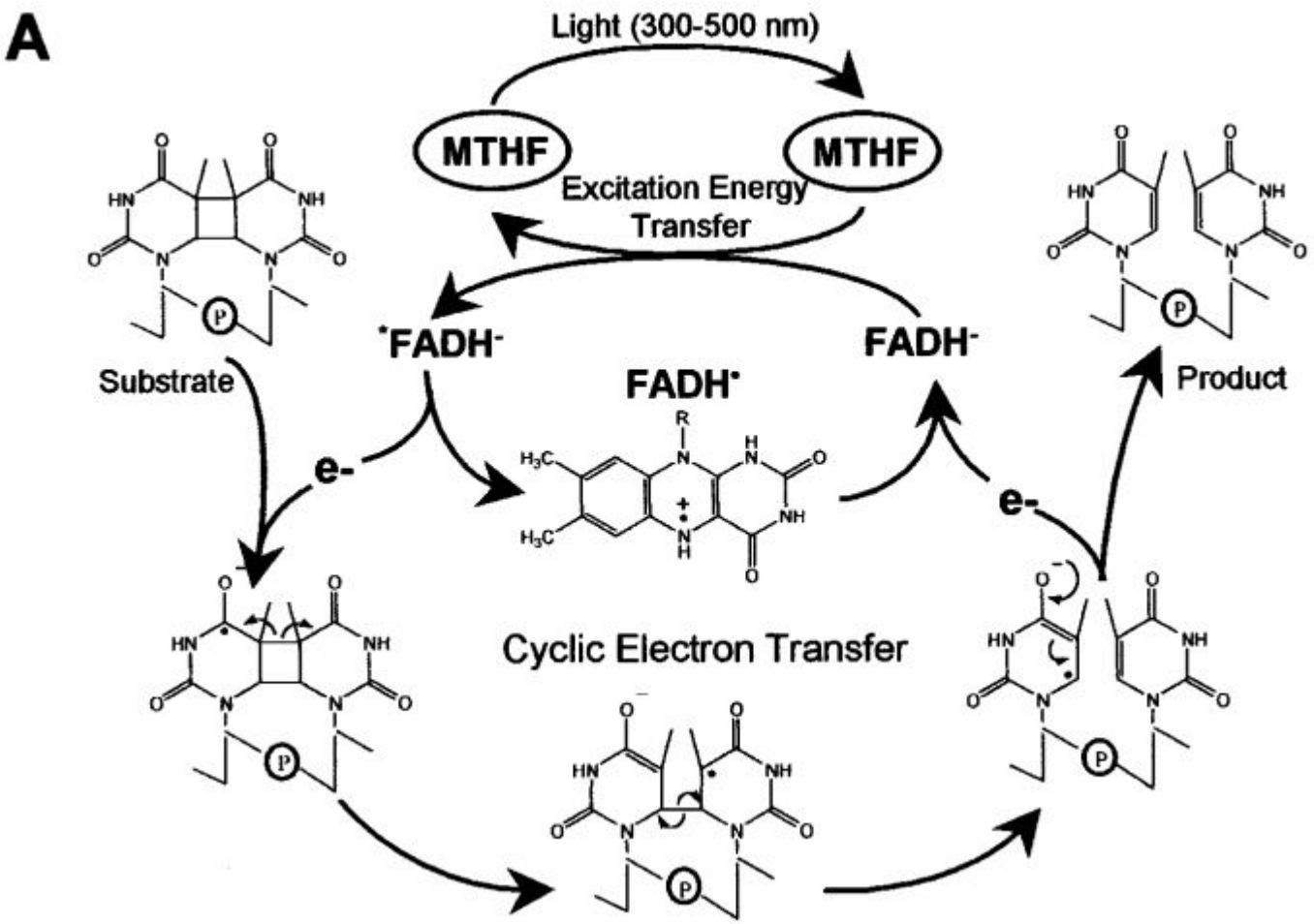


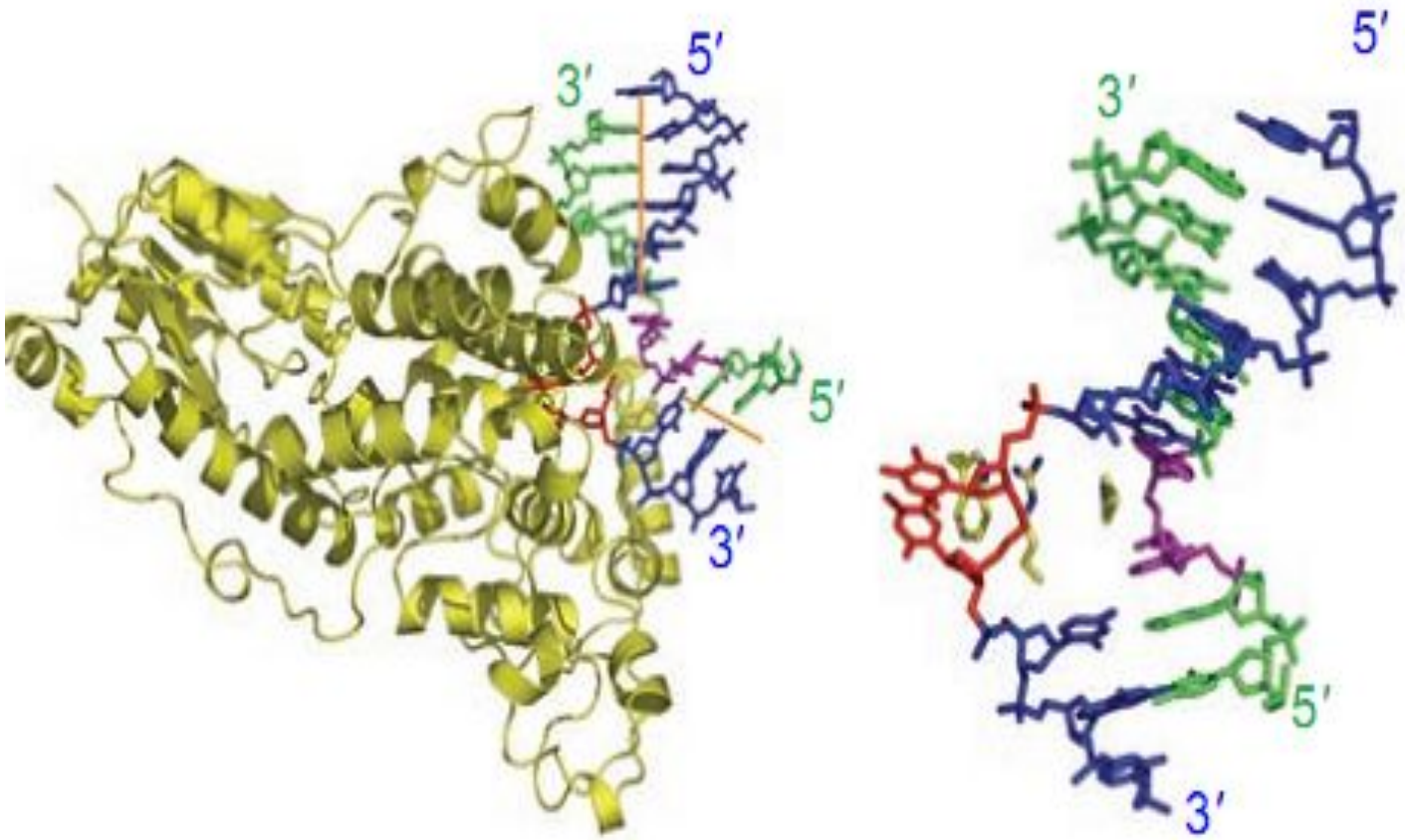


5,10-methenyltetrahydrofolate monoglutamate



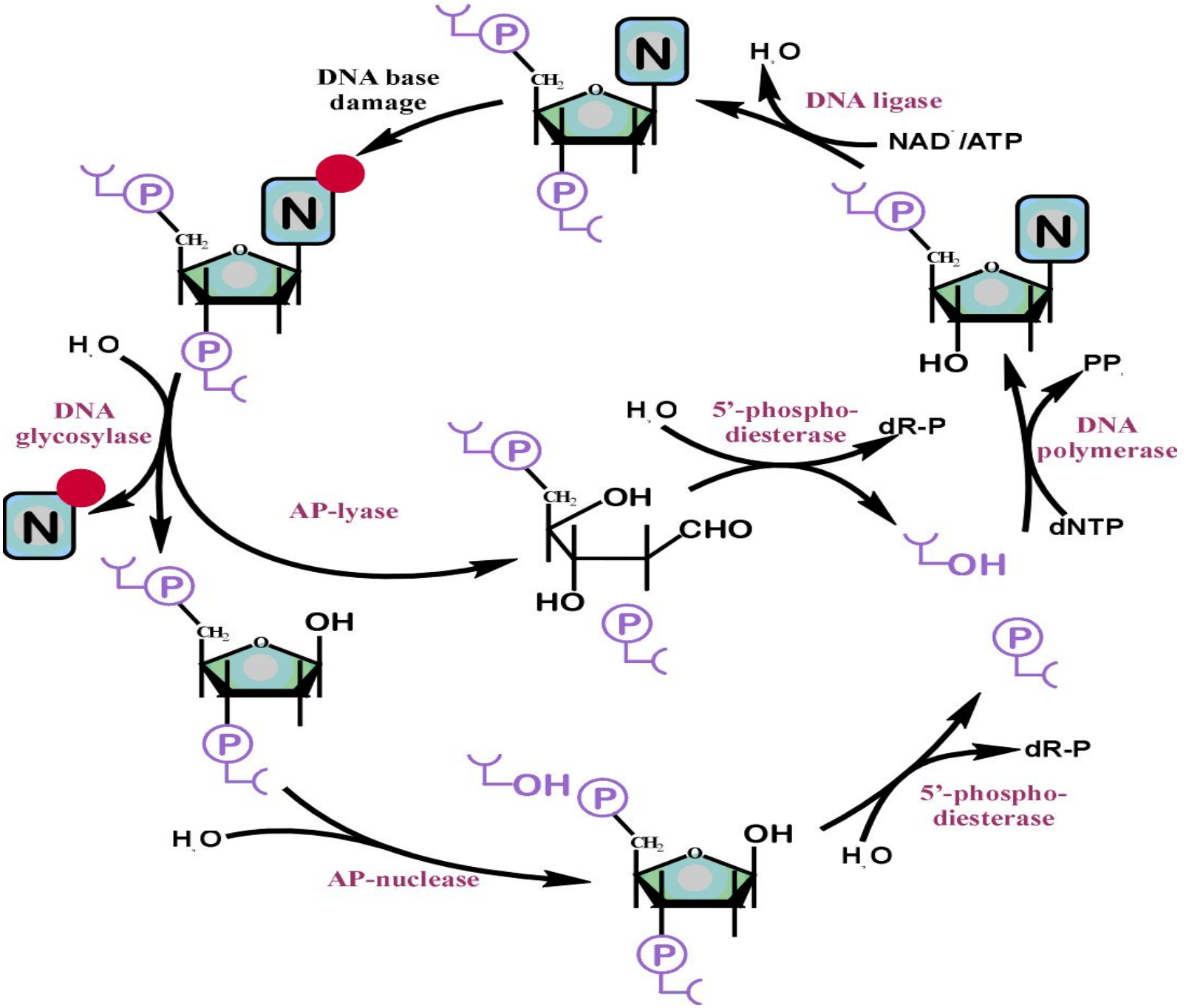
flavinadeninedinucleotide (FAD)

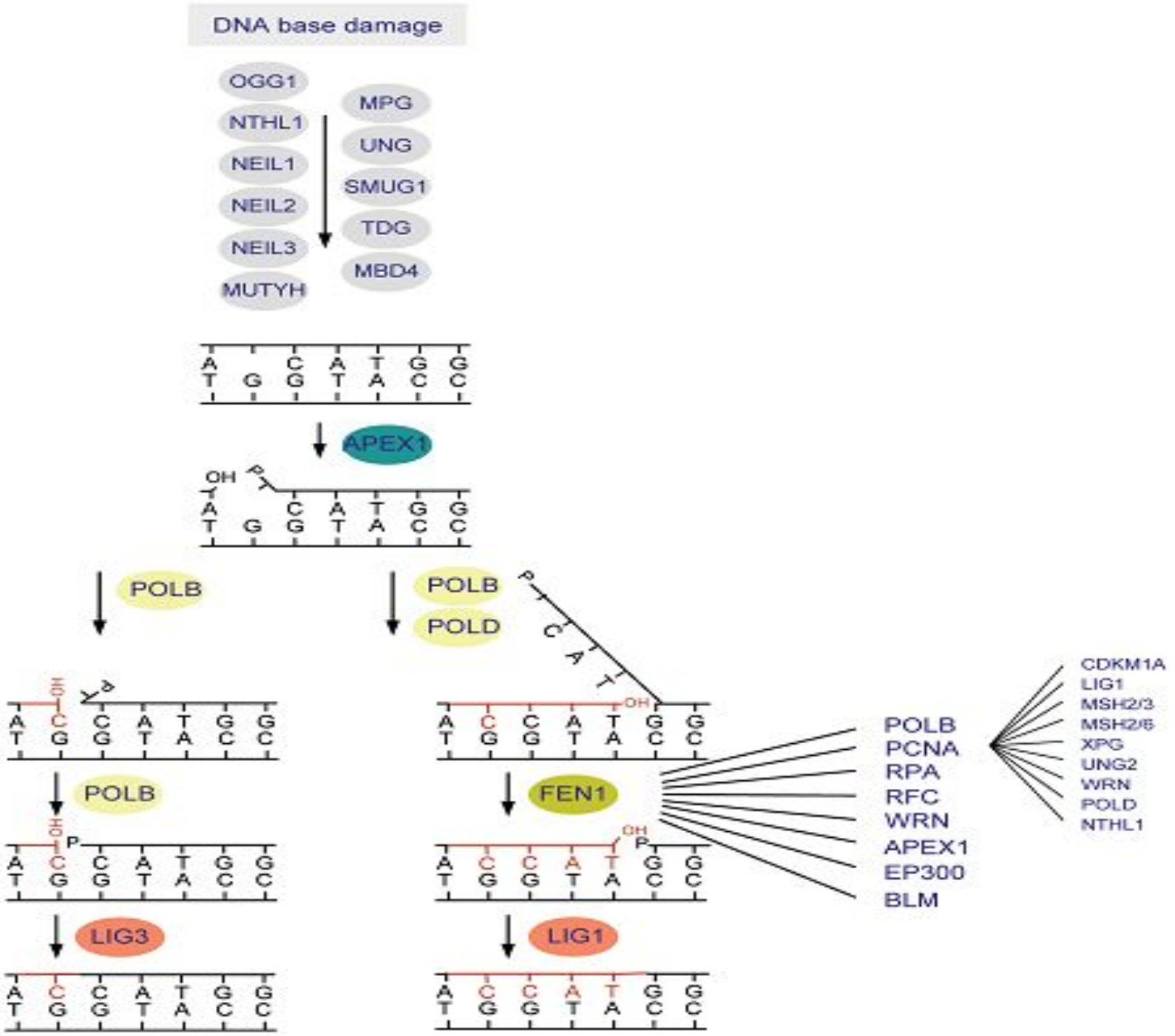

A
Light (300-500 nm)
MTHF
MTHF
Excitation Energy Transfer
*FADH-
FADH-
FADH*
Substrate
Product
e-
e-
Cyclic Electron Transfer

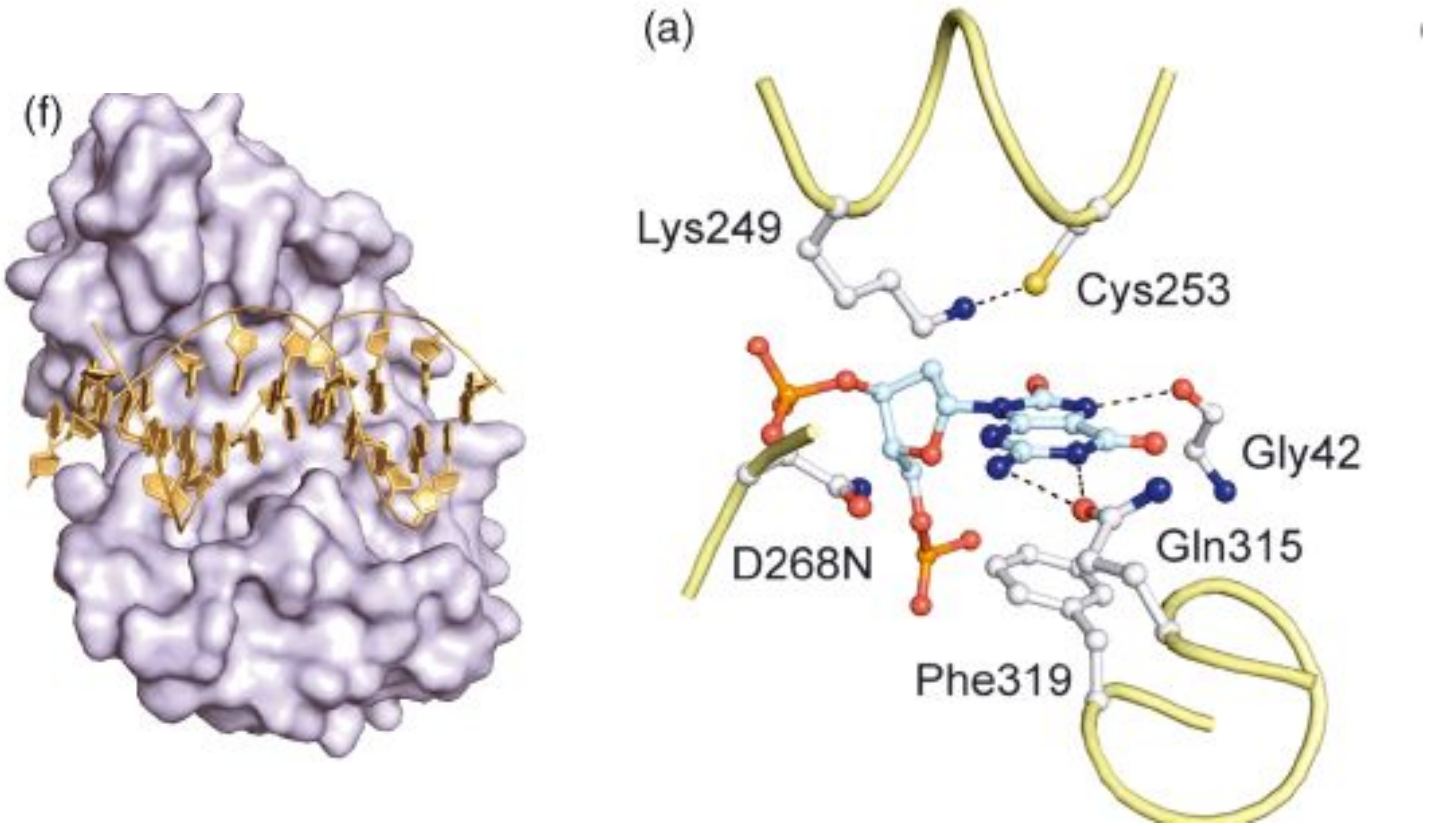


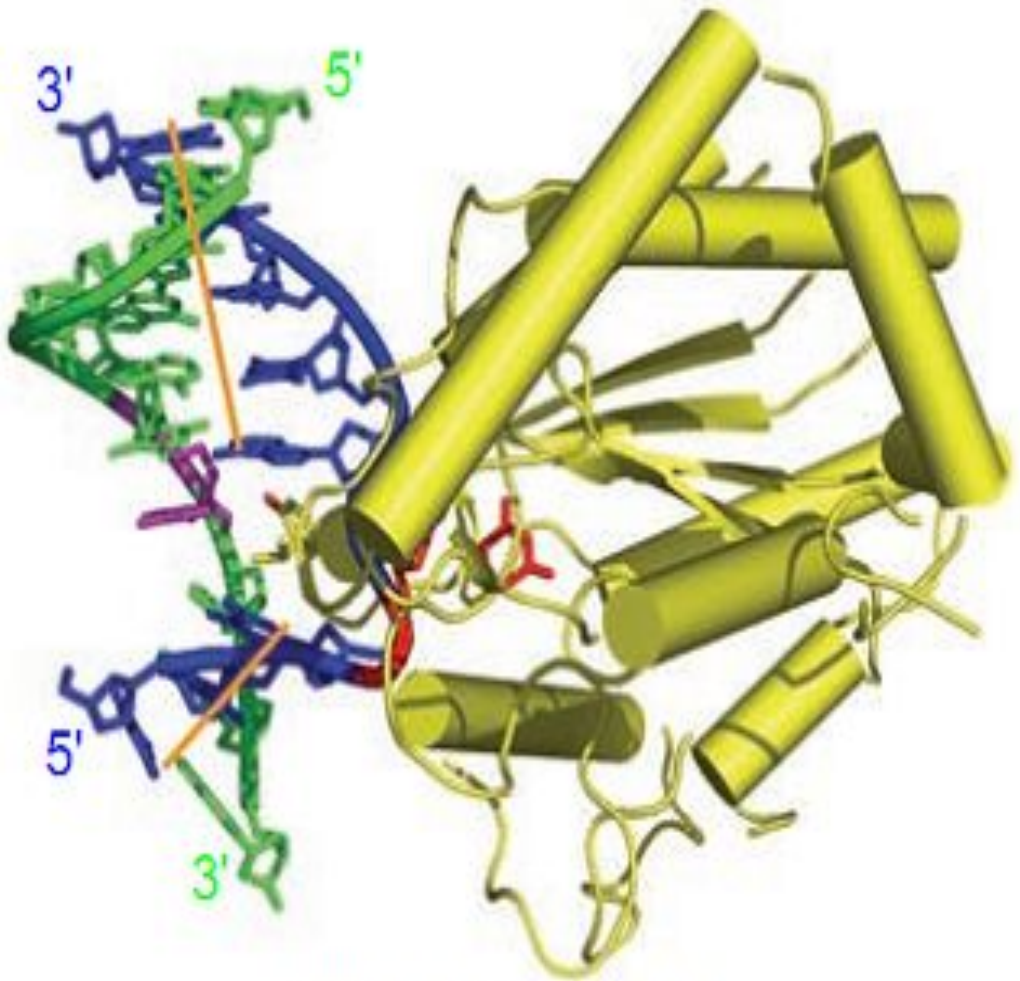
DNA Photolyase - CPD complex (1TEZ)

Base excision repair (BER)



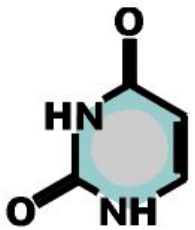

DNA base damage
OGG1
NTHL1
NEIL1
NEIL2
NEIL3
MUTYH
MPG
UNG
SMUG1
TDG
MBD4
APEX1
POLB
POLB
POLD
POLB
LIG3
FEN1
LIG1
POLB
PCNA
RPA
RFC
WRN
APEX1
EP300
BLM
CDKM1A
LIG1
MSH2/3
MSH2/6
XPG
UNG2
WRN
POLD
NTHL1


(f)
(a)
Lys249
Cys253
Gly42
D268N
Gln315
Phe319

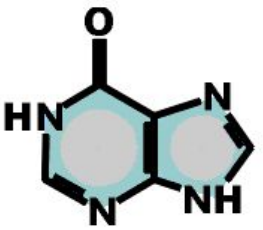


UDG-DNA (1EMJ)

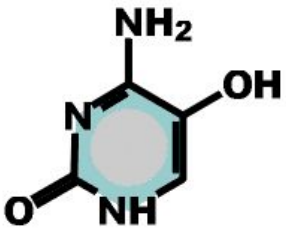
Typical DNA lesions excited by DNA glycosilases



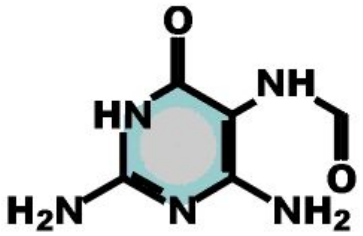
Uracil



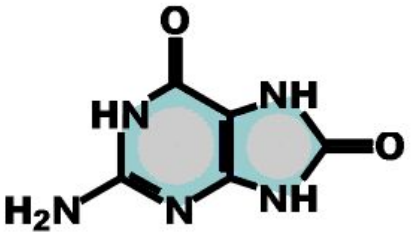
Hypoxanhtine



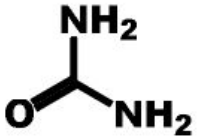
5-Hydroxycytosine



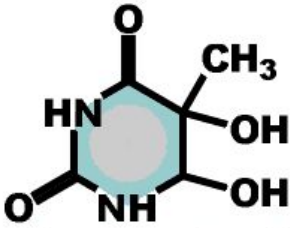
2,5-Amino-5-formamido-pyrimidine



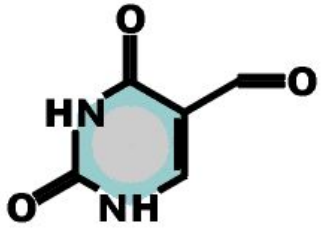
7,8-Dihidro-8-oxo-guanine



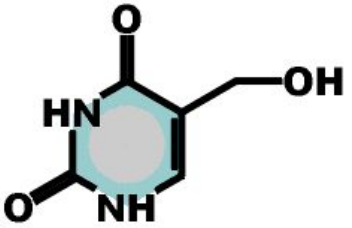
Urea



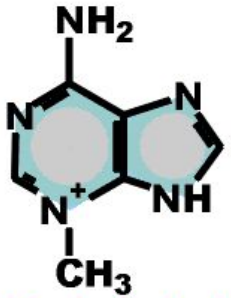
Thymine glycol



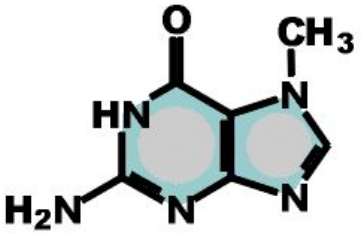
5-Formyluracil



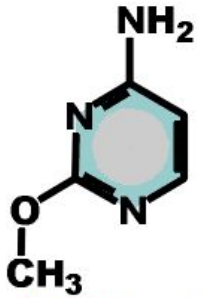
5-Hydroxymethyluracil



3-Methyladenine

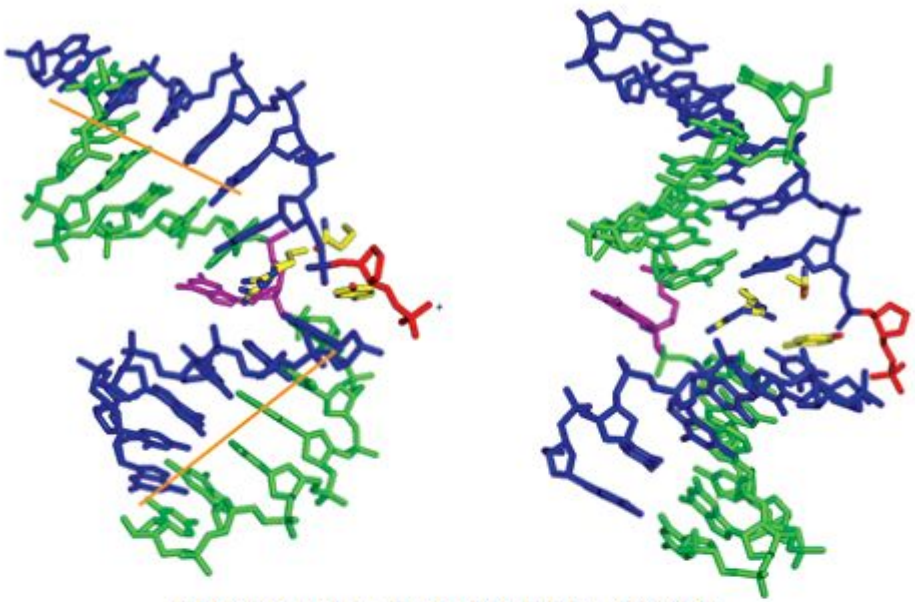


7-Methylguanine



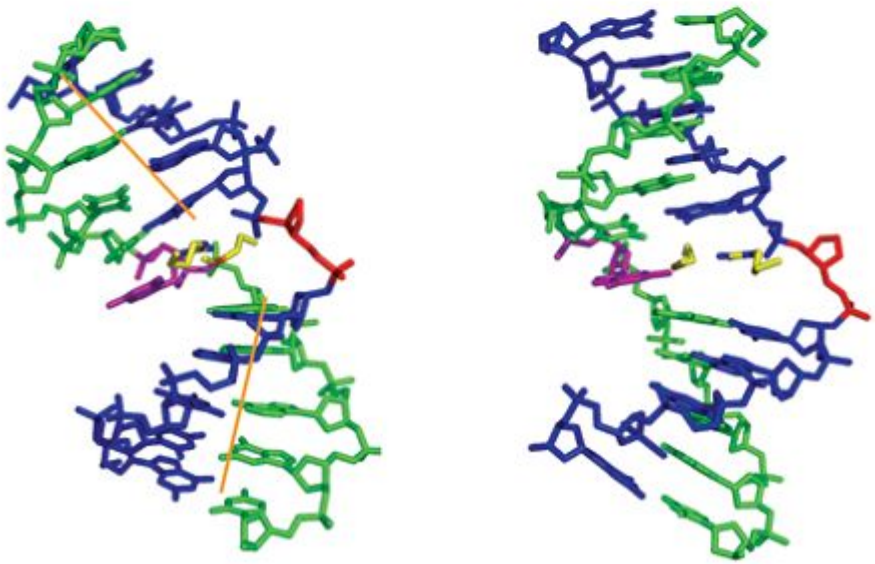
2-Methylcytosine

A



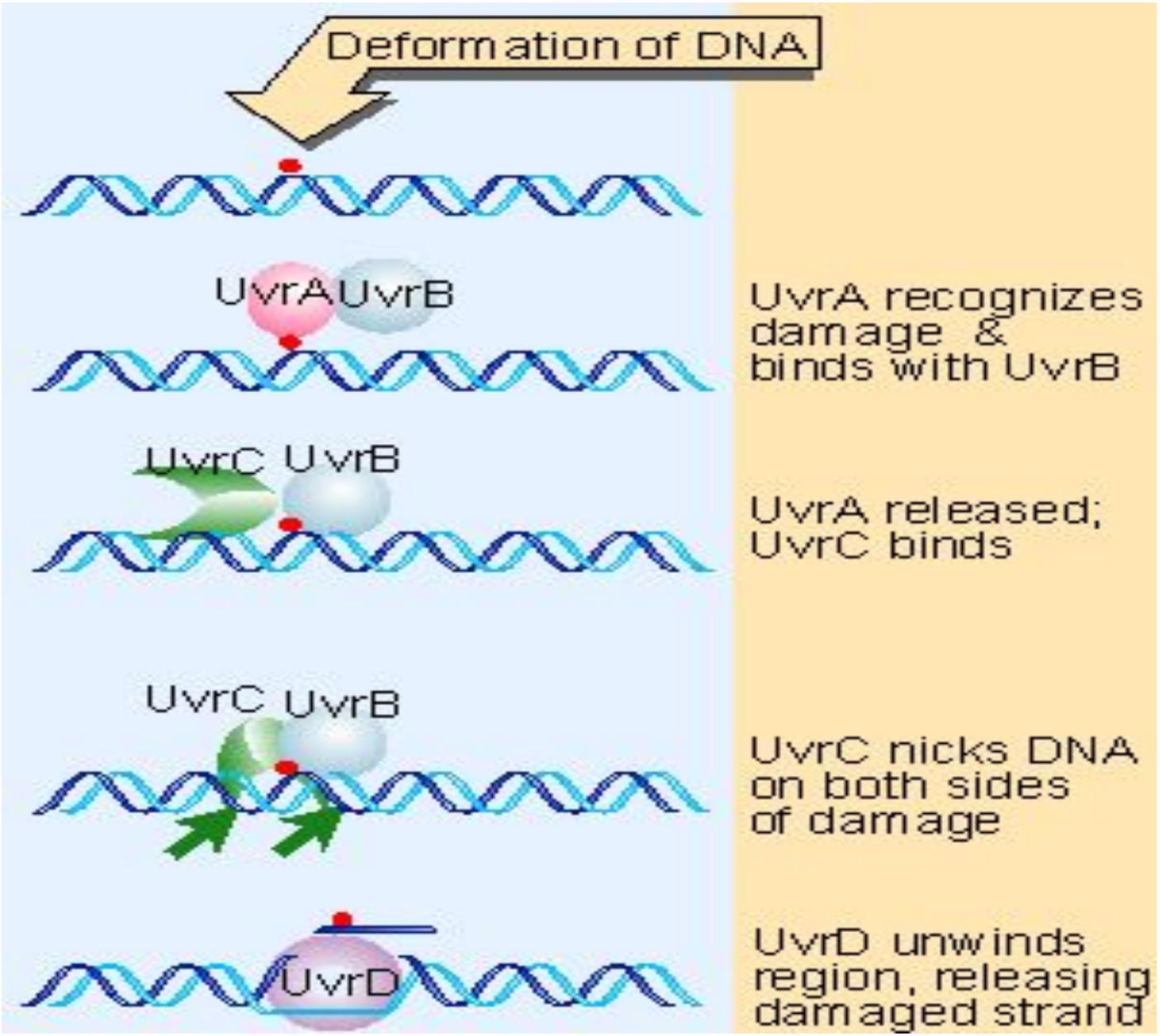
DNA bound to Endo IV (PDB: 1QUM)

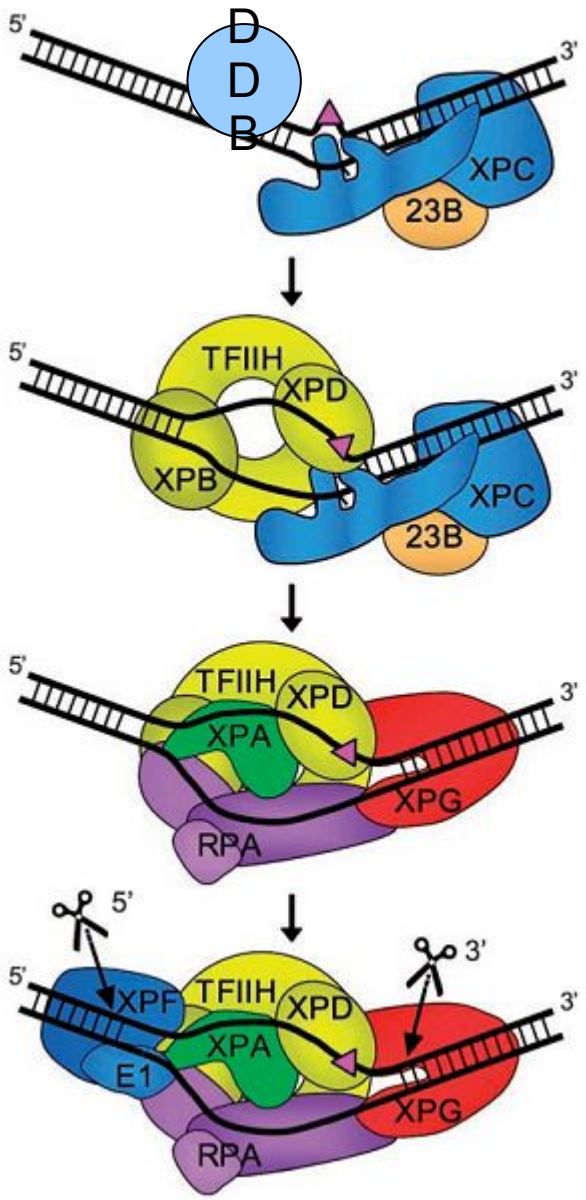
B

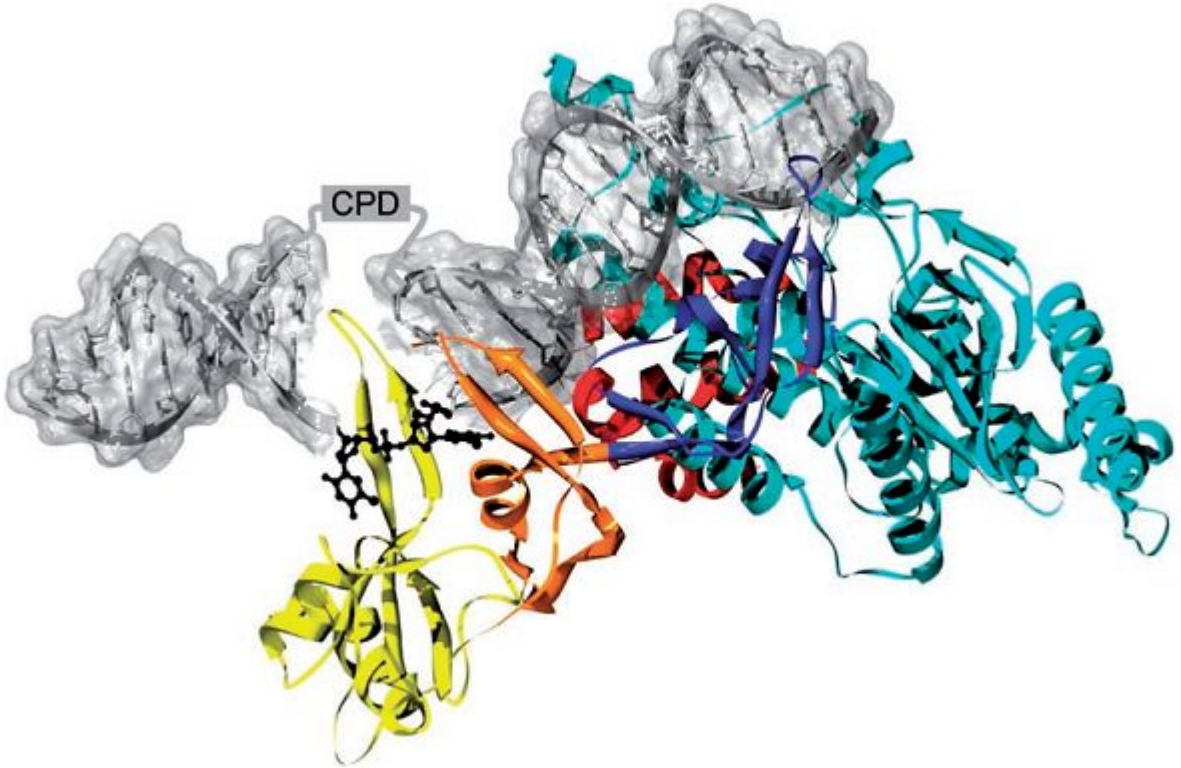


DNA bound to human APE1 (PDB: 1DE8)

NER


Deformation of DNA
UvrA UvrB
UvrA recognizes damage & binds with UvrB
UvrC UvrB
UvrA released; UvrC binds
UvrC UvrB
UvrC nicks DNA on both sides of damage
UvrD
UvrD unwinds region, releasing damaged strand


5'
3'
DDB
XPC
23B
TFIIH
XPD
XPB
XPA
XPG
RPA
XPF
E1


CPD

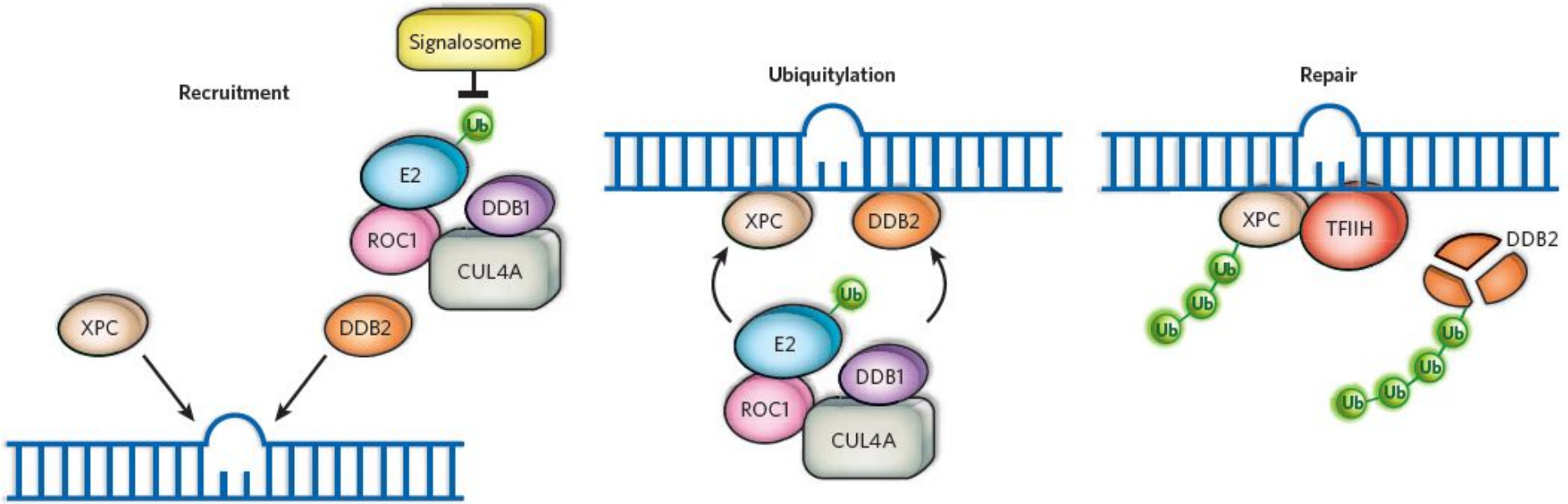


Figure 2 | Scheme for XPC and DDB2 ubiquitylation. Helix-distorting lesions are substrates for XPC and DDB2 (left). XPC binds to the undamaged strands of helix-distorted lesions (middle). DDB2 becomes part of a larger, cullin 4a-based E3 ubiquitin ligase complex (CUL4a, DDB1, ROC1 and an E2 ubiquitin-conjugating enzyme). In the absence of DNA damage, the ubiquitylation activity is repressed by the signalosome (COP9) complex (upper left). Upon DNA damage, the signalosome dissociates, allowing the DDB2–E3 ligase complex to bind to the damaged site. Both XPC and DDB2 are substrates of the ubiquitin ligase; however, whereas DDB2 is degraded, XPC is not (right). The role of XPC ubiquitylation is currently not known, but it may promote specific protein interactions.

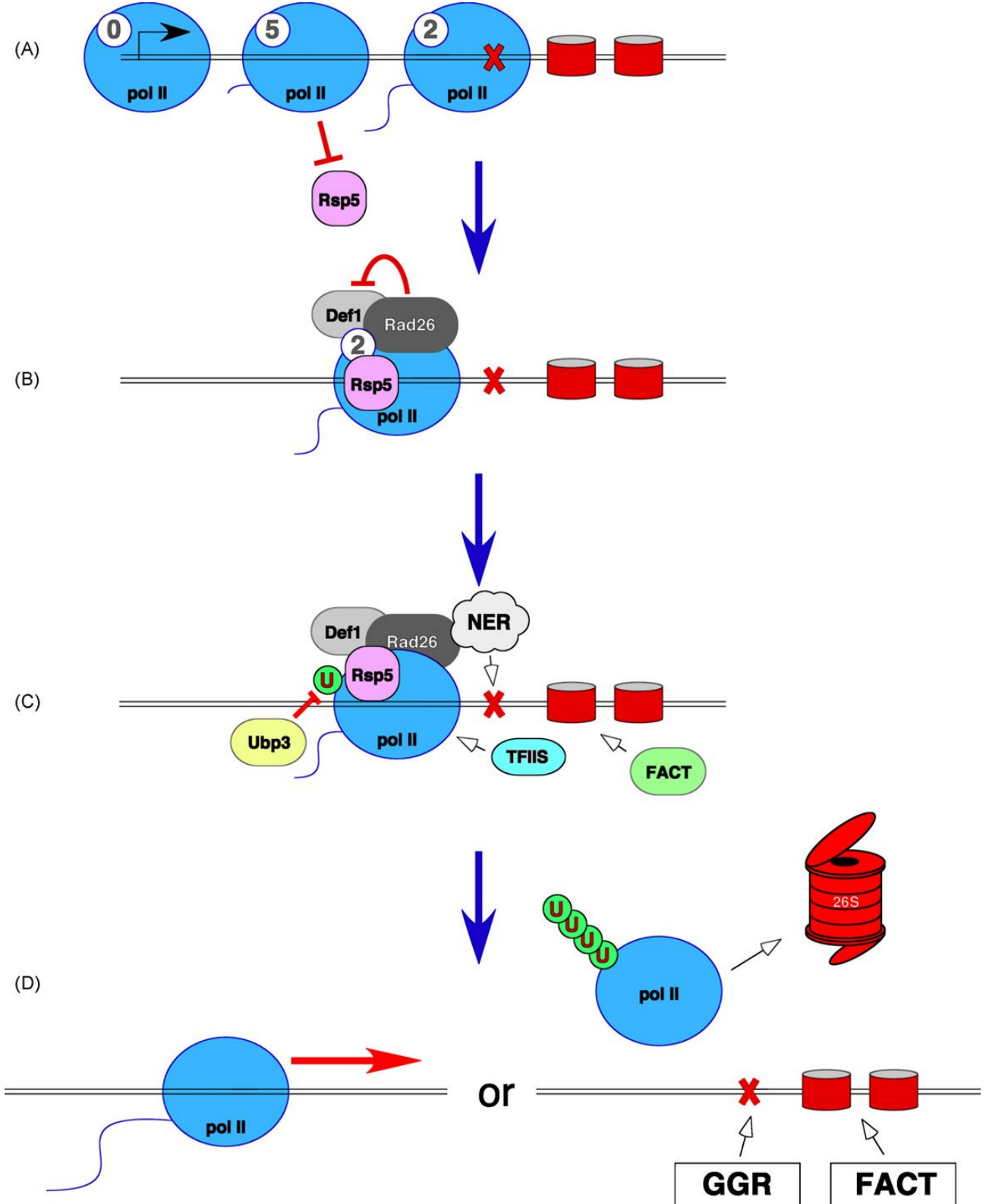
GG-NER

XPC

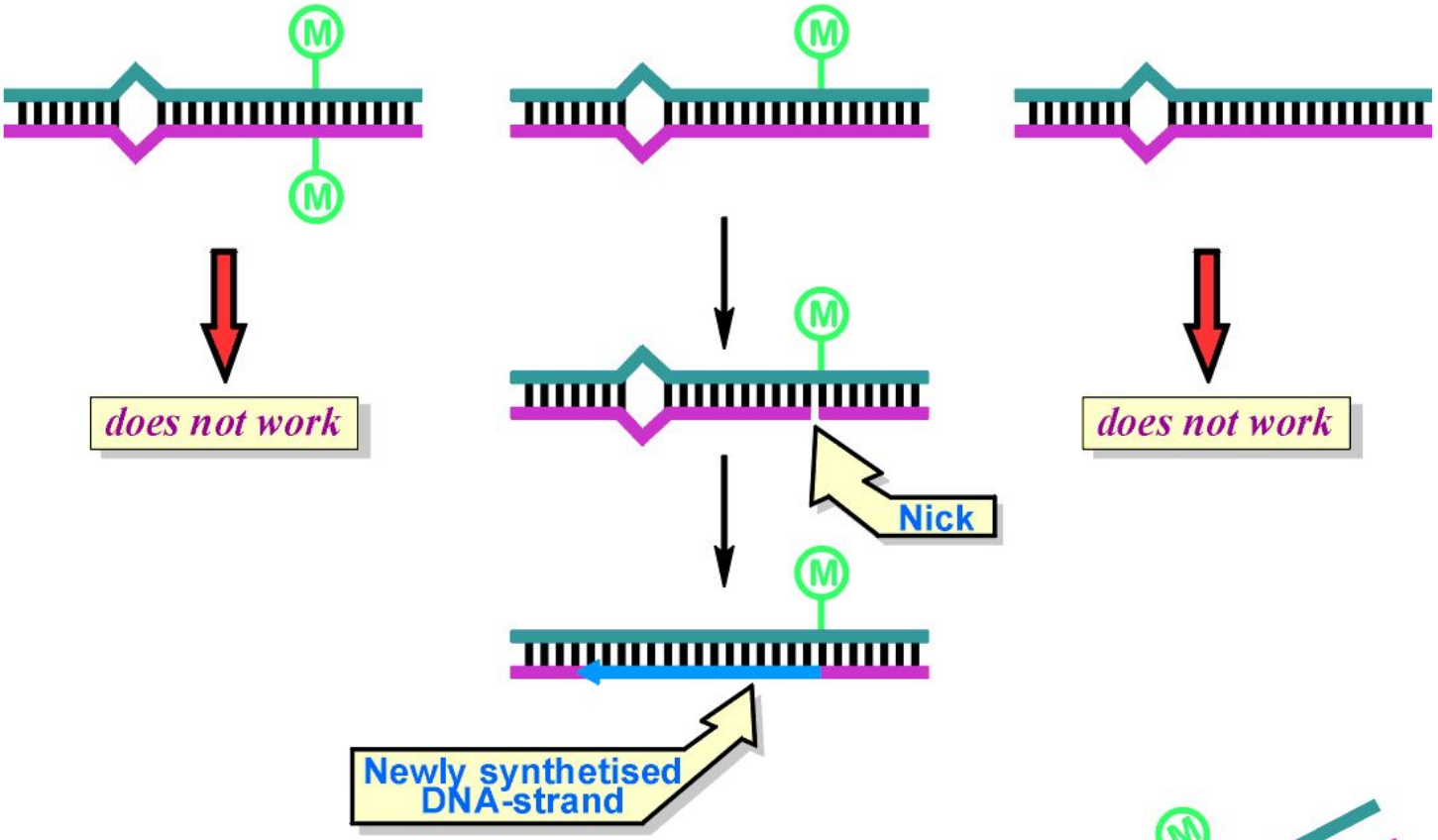
UV-DDB

TC-NER

CSA, CSB
DCAF family
and ???

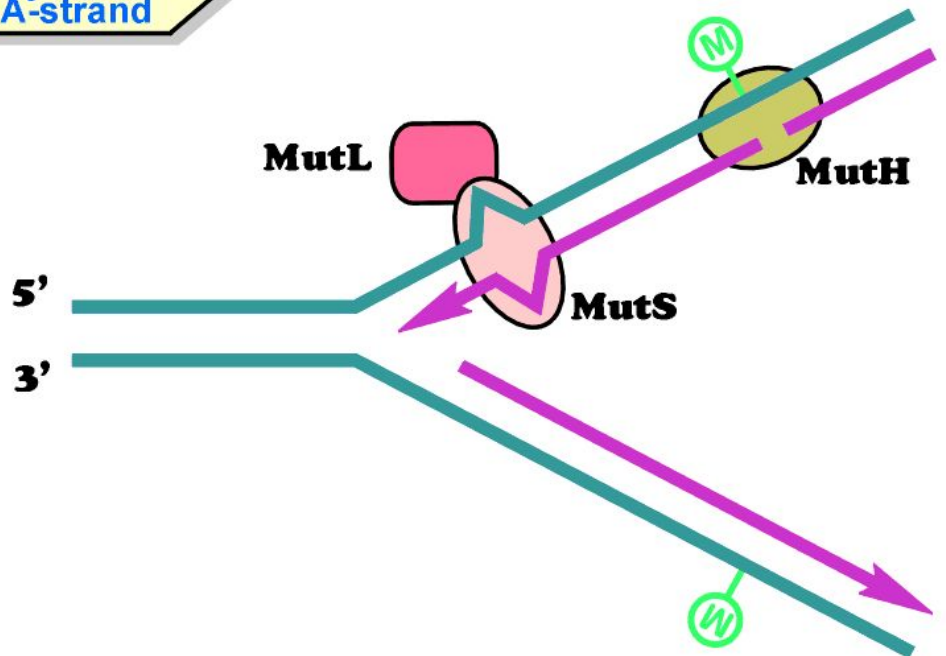

(A)
0
pol II
5
pol II
2
pol II
Rsp5
(B)
Def1
Rad26
2
Rsp5
pol II
(C)
Def1
Rad26
NER
U
Rsp5
Ubp3
pol II
TFIIS
FACT
(D)
U U U
pol II
26S
pol II
or
GGR
FACT

Mismatch repair

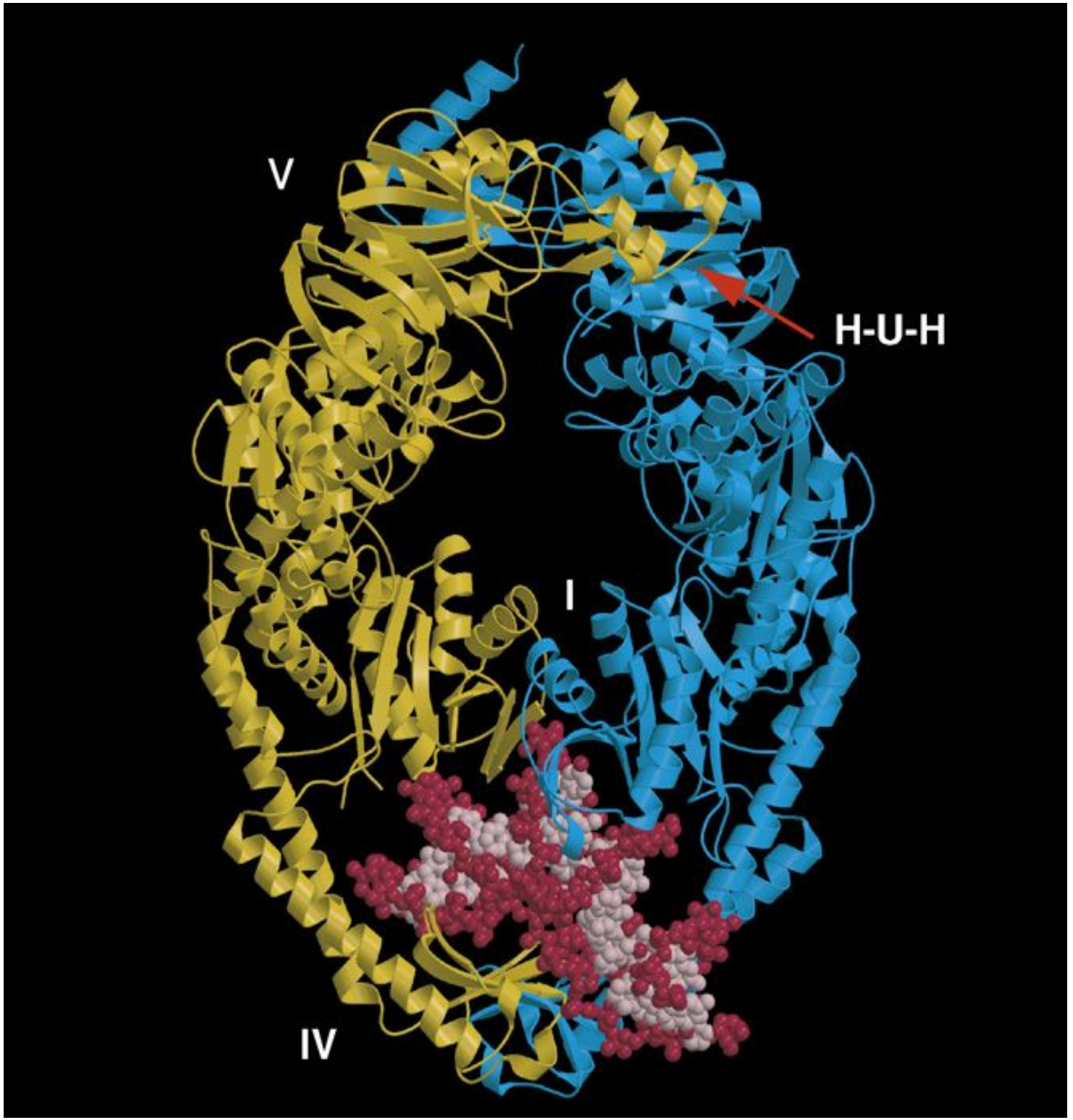


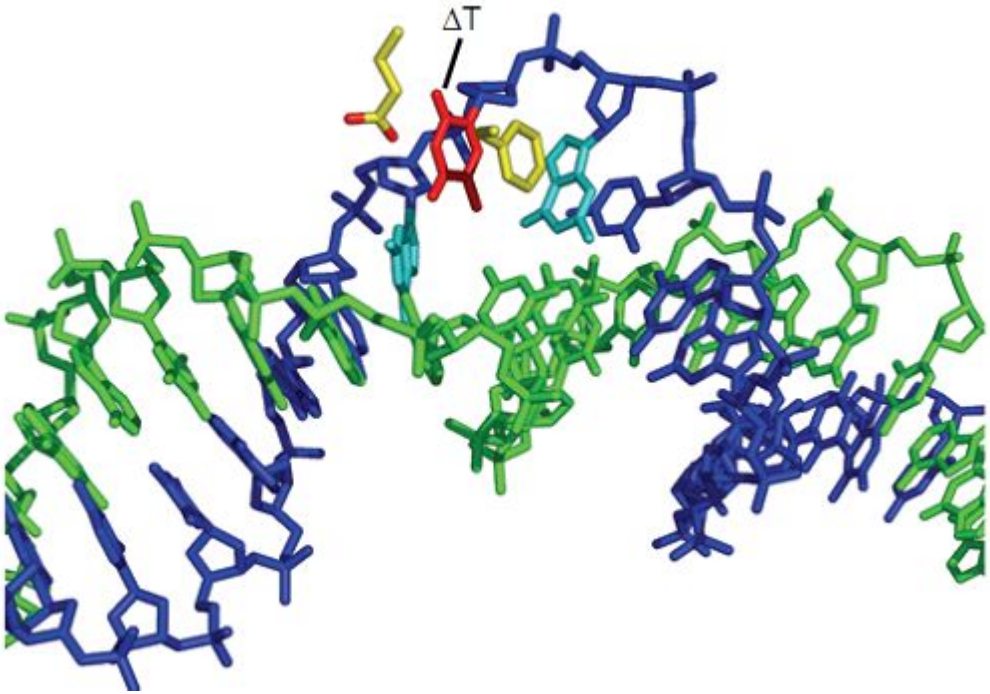
Excision / resynthesis

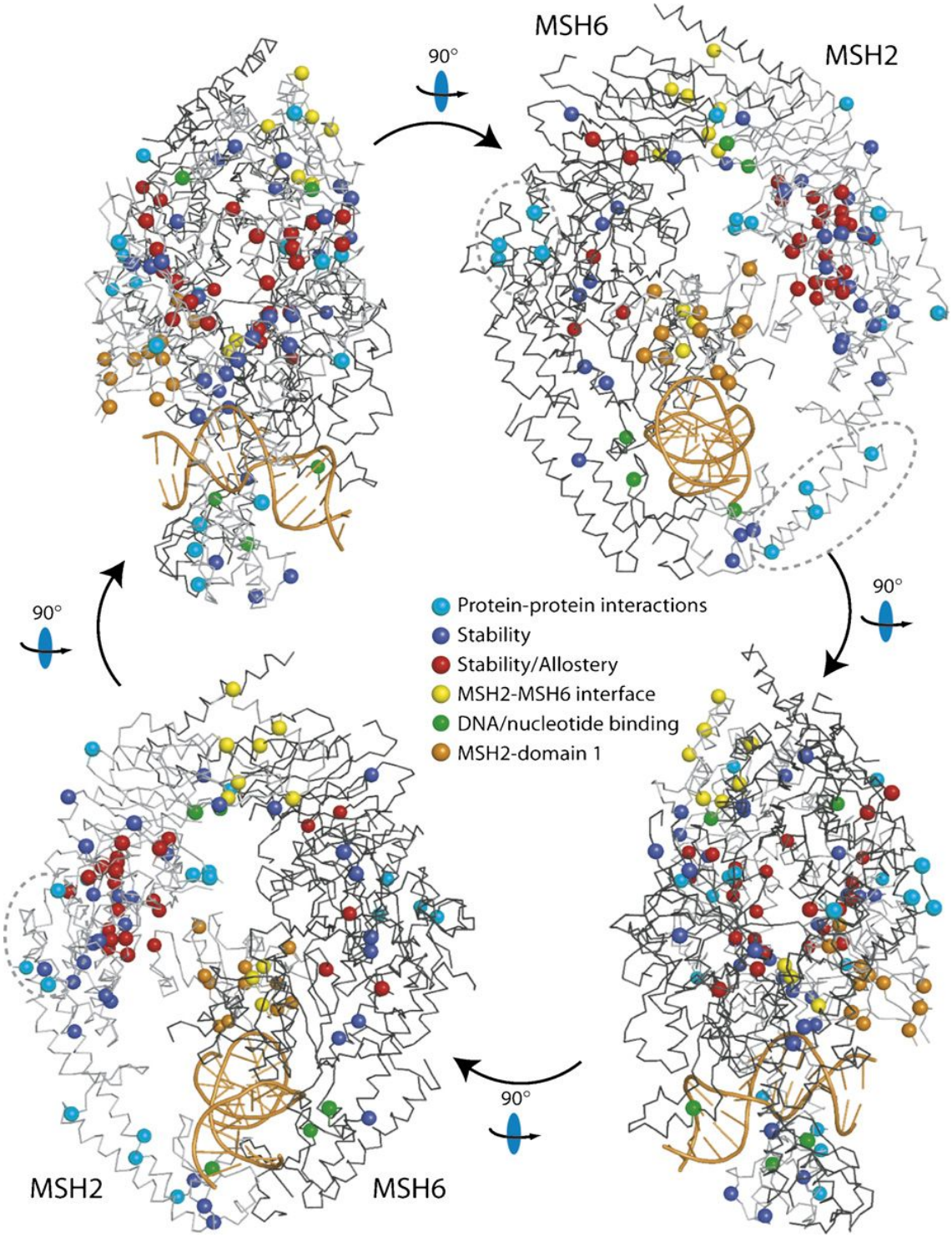
Exo I, Exo VII or RecJ,
Helicase II,
DNA pol III, SSB and
DNA ligase

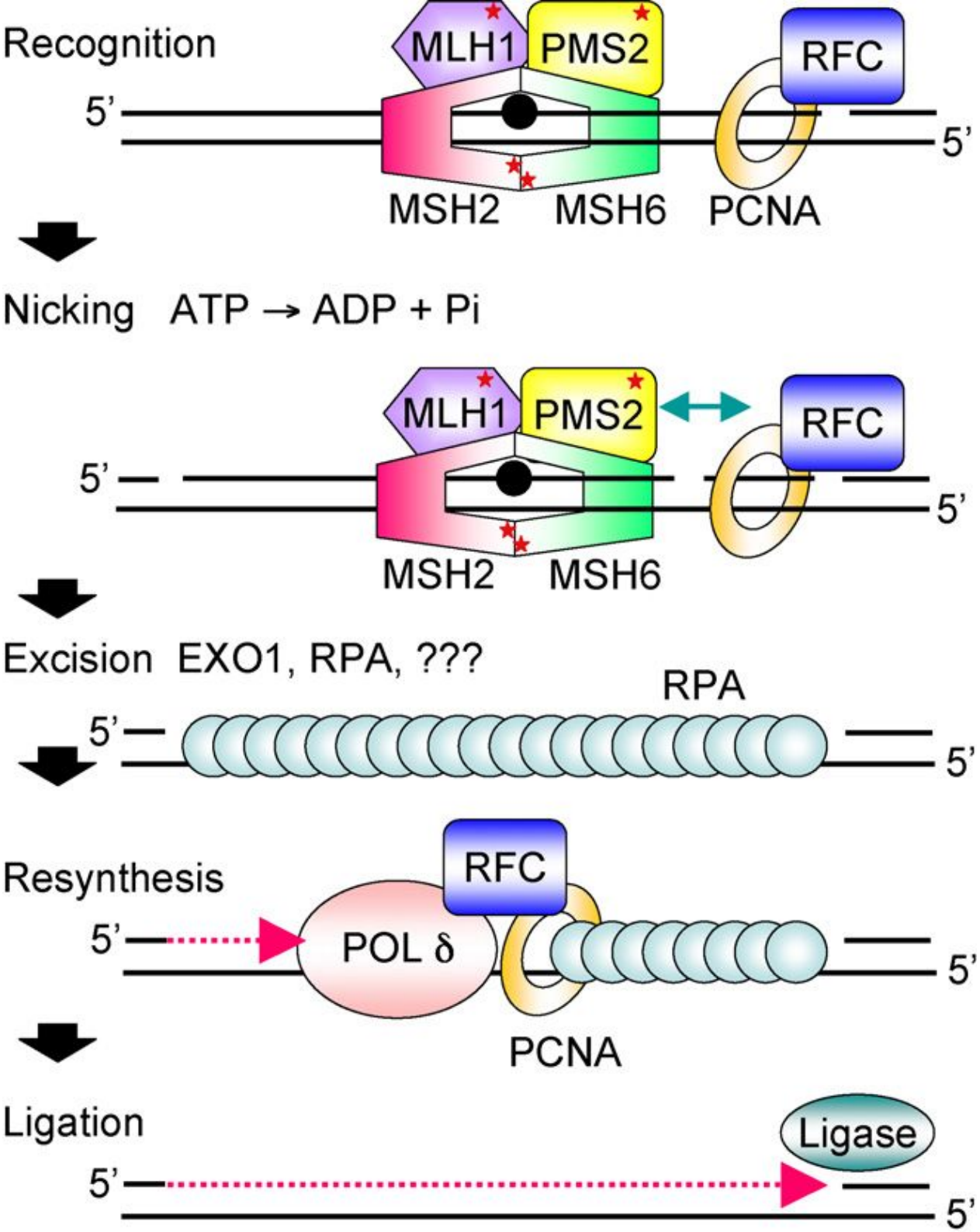


MutS

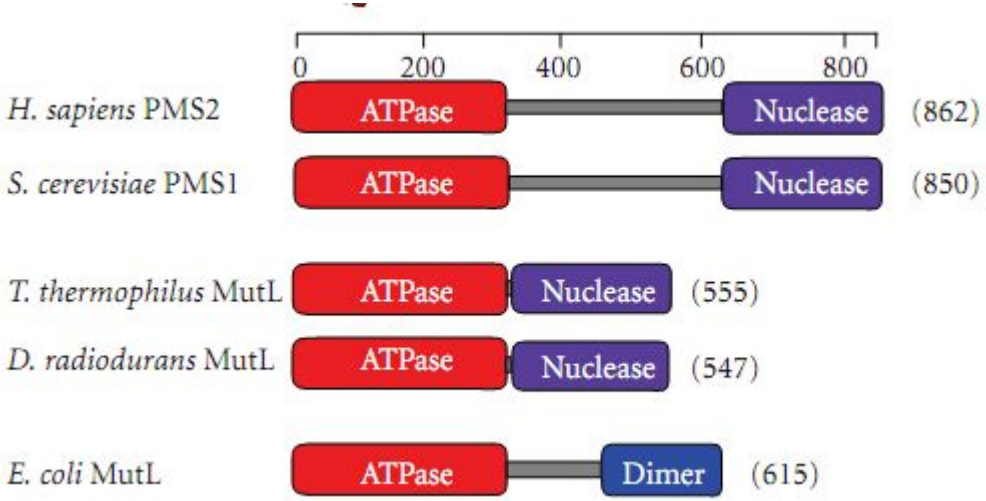


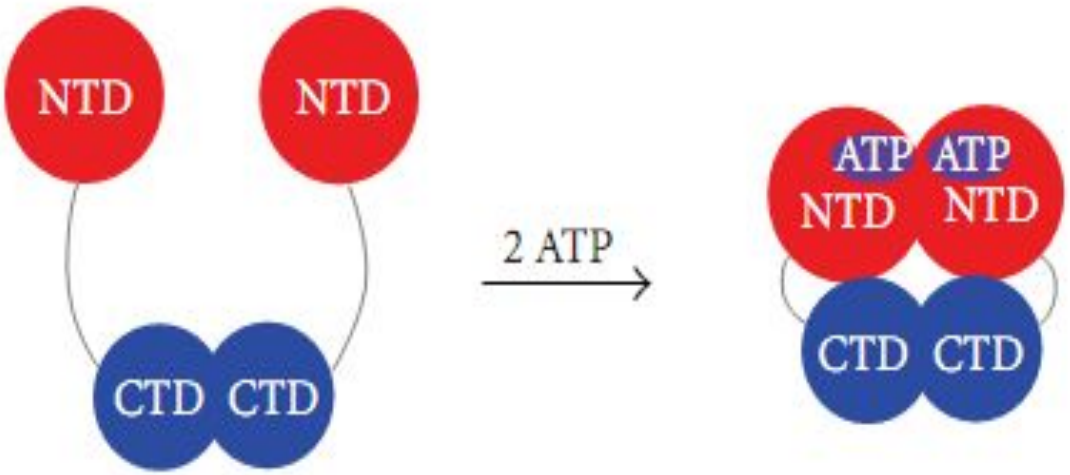

ΔT


MSH6
MSH2
90°
90°
90°
90°
Protein-protein interactions
Stability
Stability/Allostery
MSH2-MSH6 interface
DNA/nucleotide binding
MSH2-domain 1
MSH2
MSH6

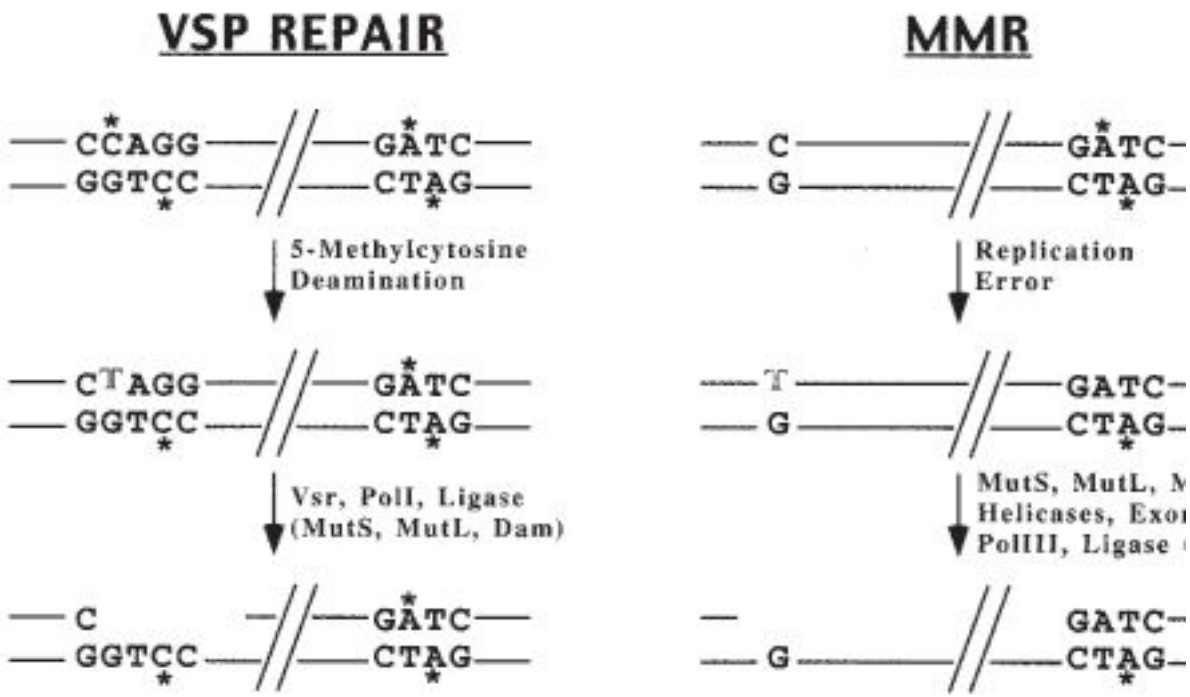

Recognition
MLH1
PMS2
RFC
5'
5'
MSH2
MSH6
PCNA
Nicking ATP → ADP + Pi
MLH1
PMS2
RFC
5'
5'
MSH2
MSH6
Excision EXO1, RPA, ???
RPA
5'
5'
Resynthesis
RFC
5'
POL δ
5'
PCNA
Ligation
Ligase
5'
5'

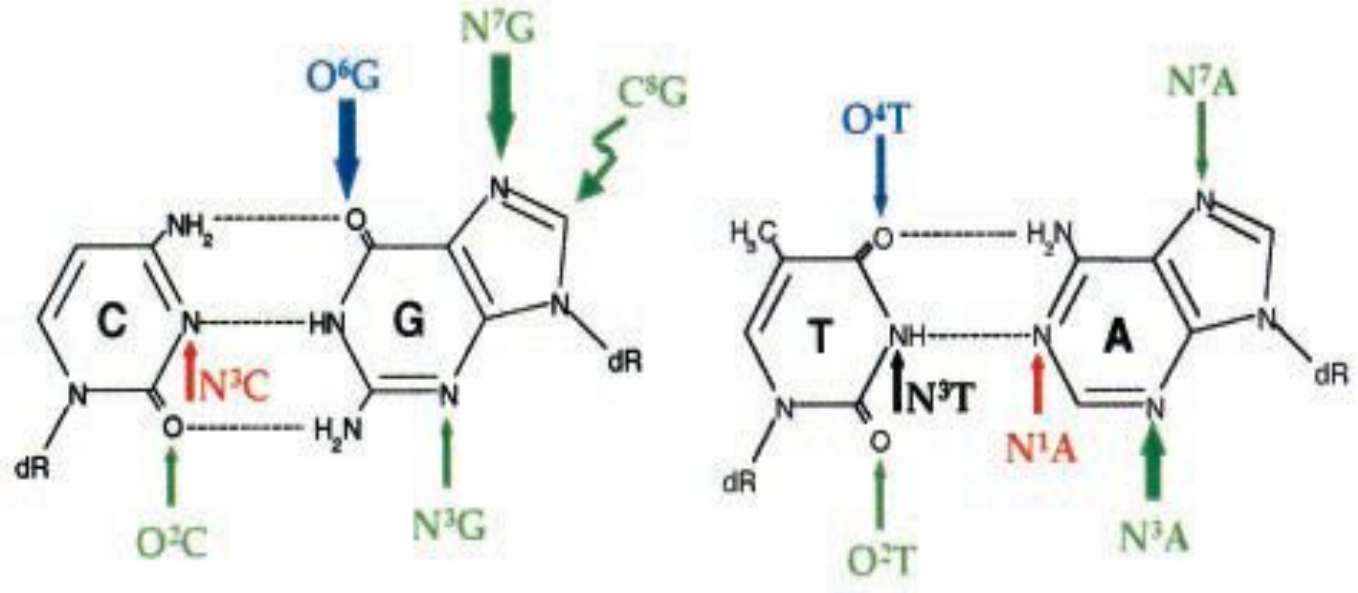
MutLa

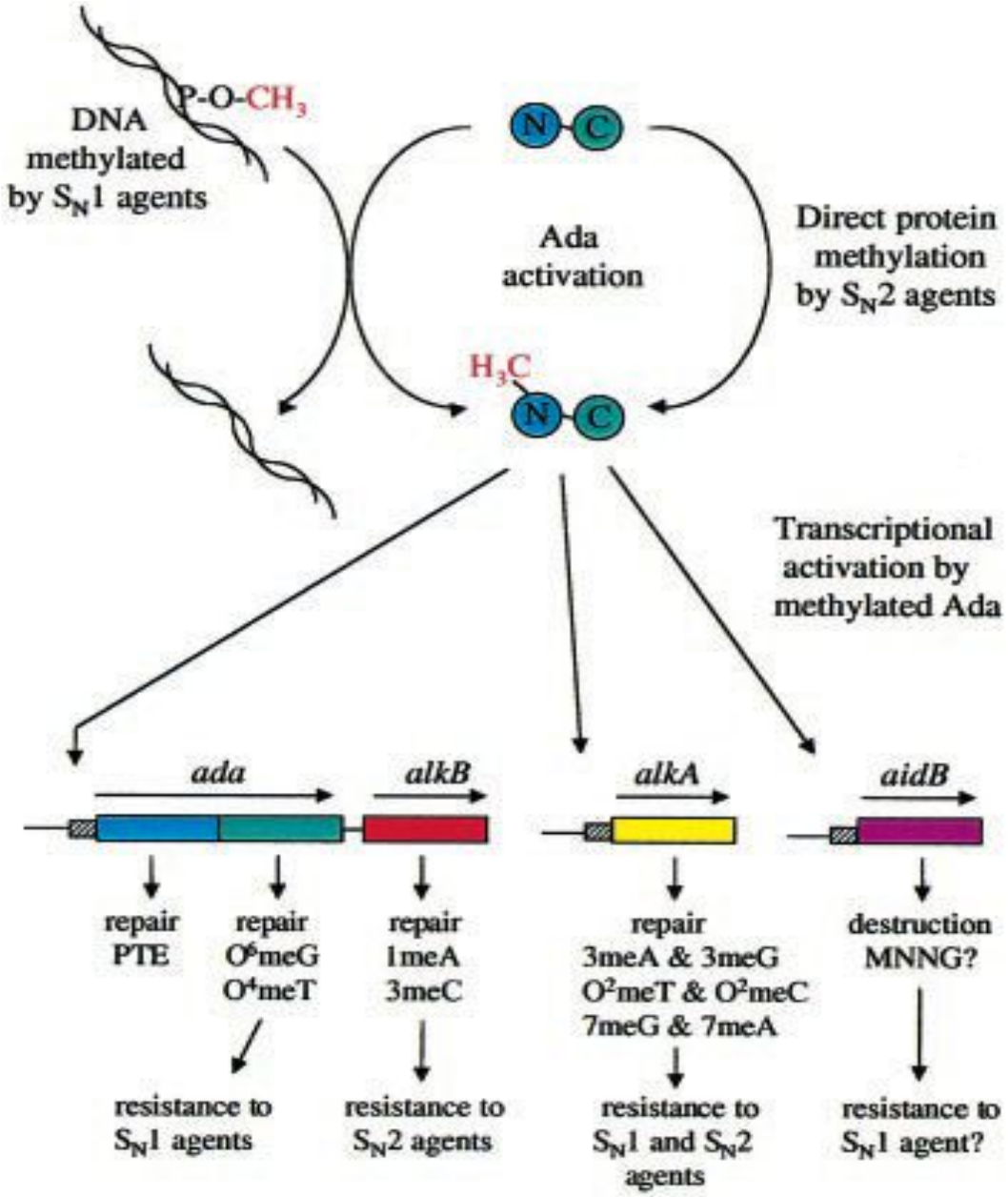




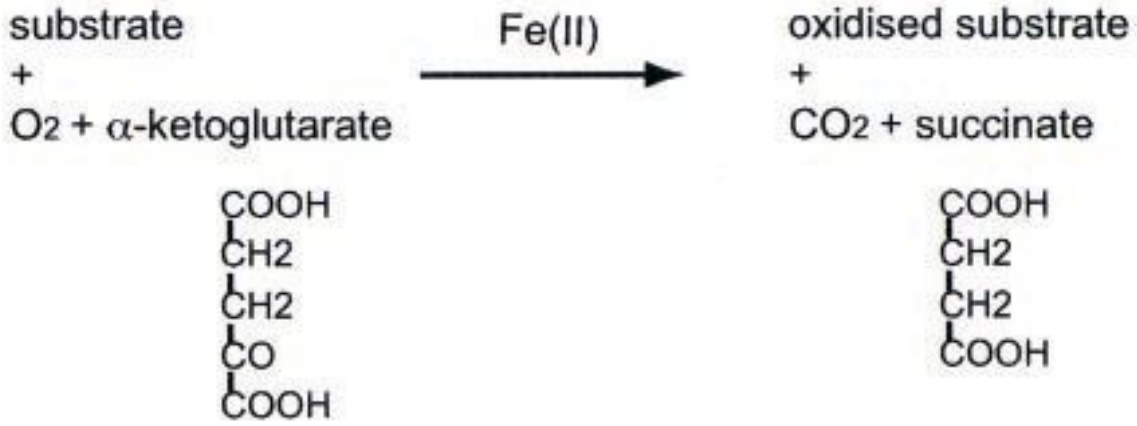
of MutLα, the PMS2 and MLH1 subunits dimerize via their C-terminal domains. ATP binding induces the dimerization of the N-terminal domain and condensation of the molecule.


VSP REPAIR
MMR
5-Methylcytosine
Deamination
Vsr, PolI, Ligase
(MutS, MutL, Dam)
Replication
Error
MutS, MutL, M
Helicases, Exo
PolIII, Ligase

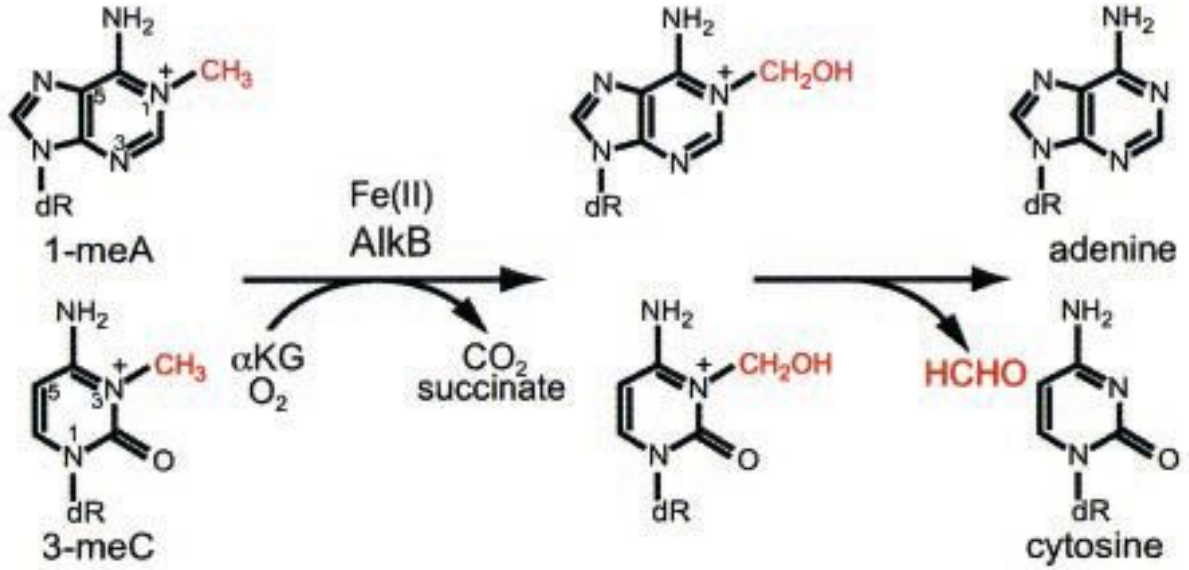

N7G
O6G
C8G
NH2
O
N
C
N
HN
G
N
dR
N3C
N
O
H2N
N
dR
O2C
N3G
O4T
N7A
H3C
O
H2N
N
T
NH
N
A
N
dR
N3T
N1A
N
O
dR
O2T
N3A

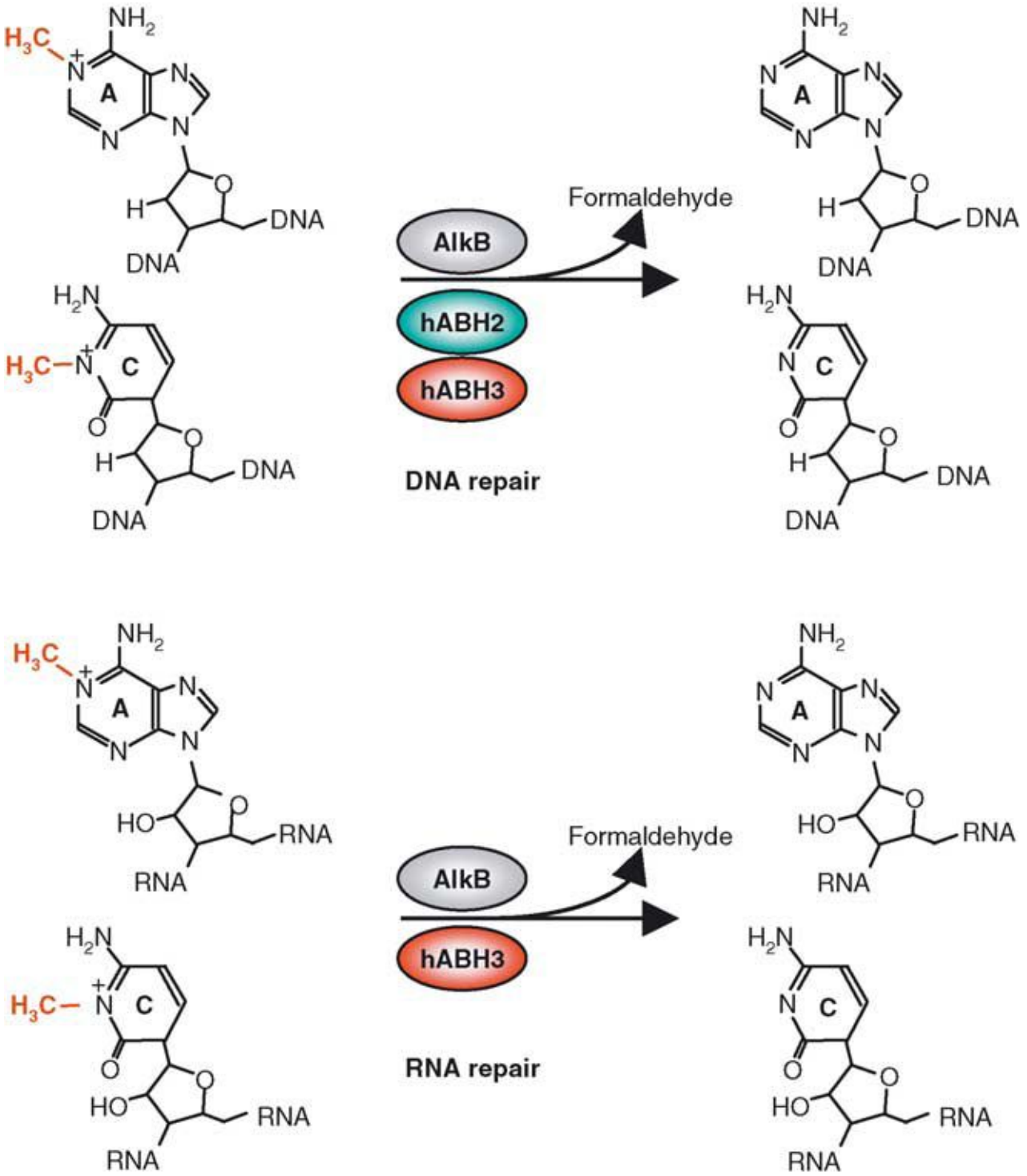

P-O-CH3
DNA
methylated
by SN1 agents
N
C
Ada
activation
Direct protein
methylation
by SN2 agents
H3C
N
C
Transcriptional
activation by
methylated Ada
ada
alkB
alkA
aidB
repair
PTE
repair
O6meG
O4meT
repair
1meA
3meC
repair
3meA & 3meG
O2meT & O2meC
7meG & 7meA
destruction
MNNG?
resistance to
SN1 agents
resistance to
SN2 agents
resistance to
SN1 and SN2
agents
resistance to
SN1 agent?

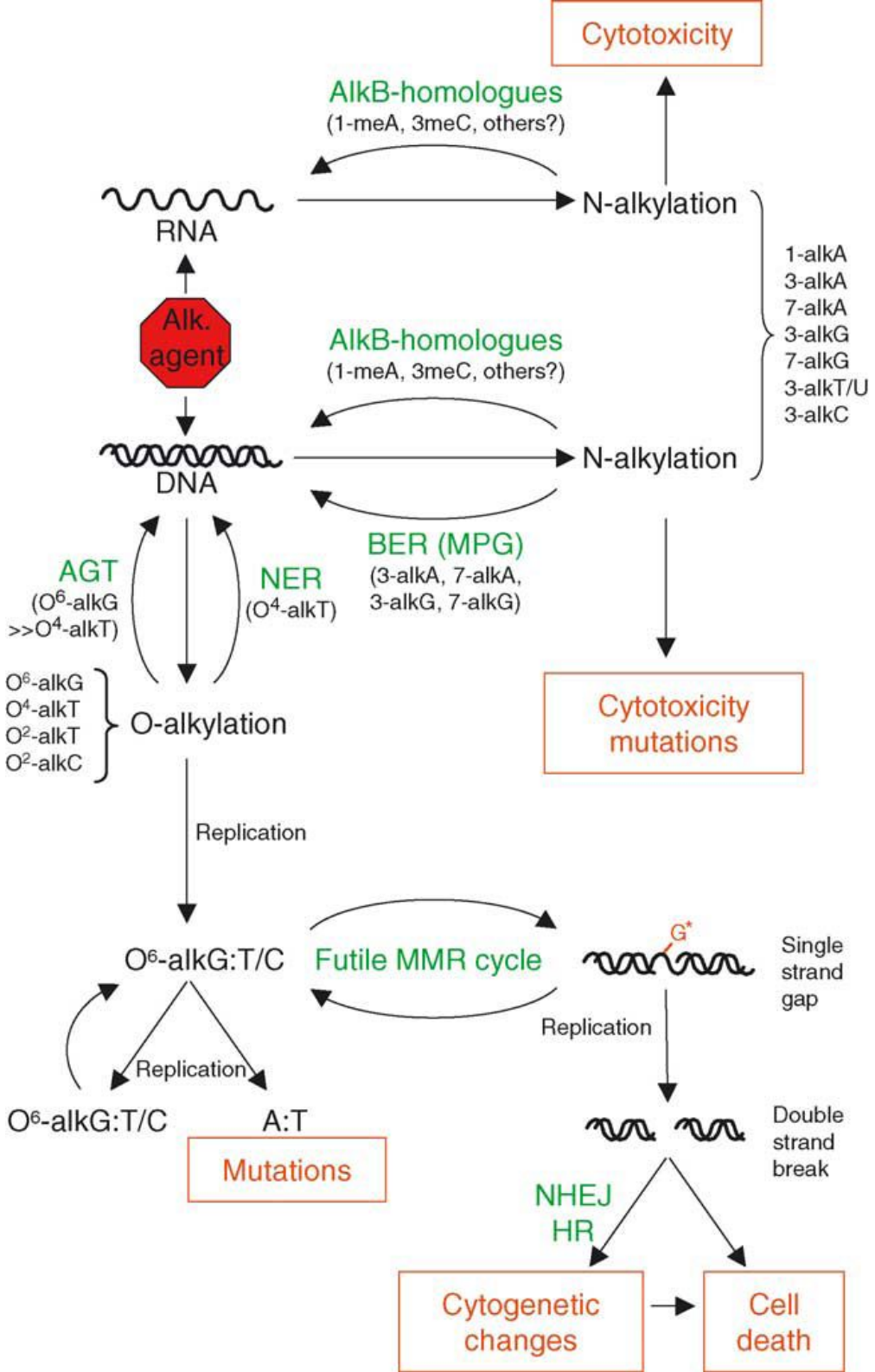
A.


substrate
+
O2 + α-ketoglutarate
Fe(II)
oxidised substrate
+
CO2 + succinate
COOH
CH2
CH2
CO
COOH
COOH
CH2
CH2
COOH

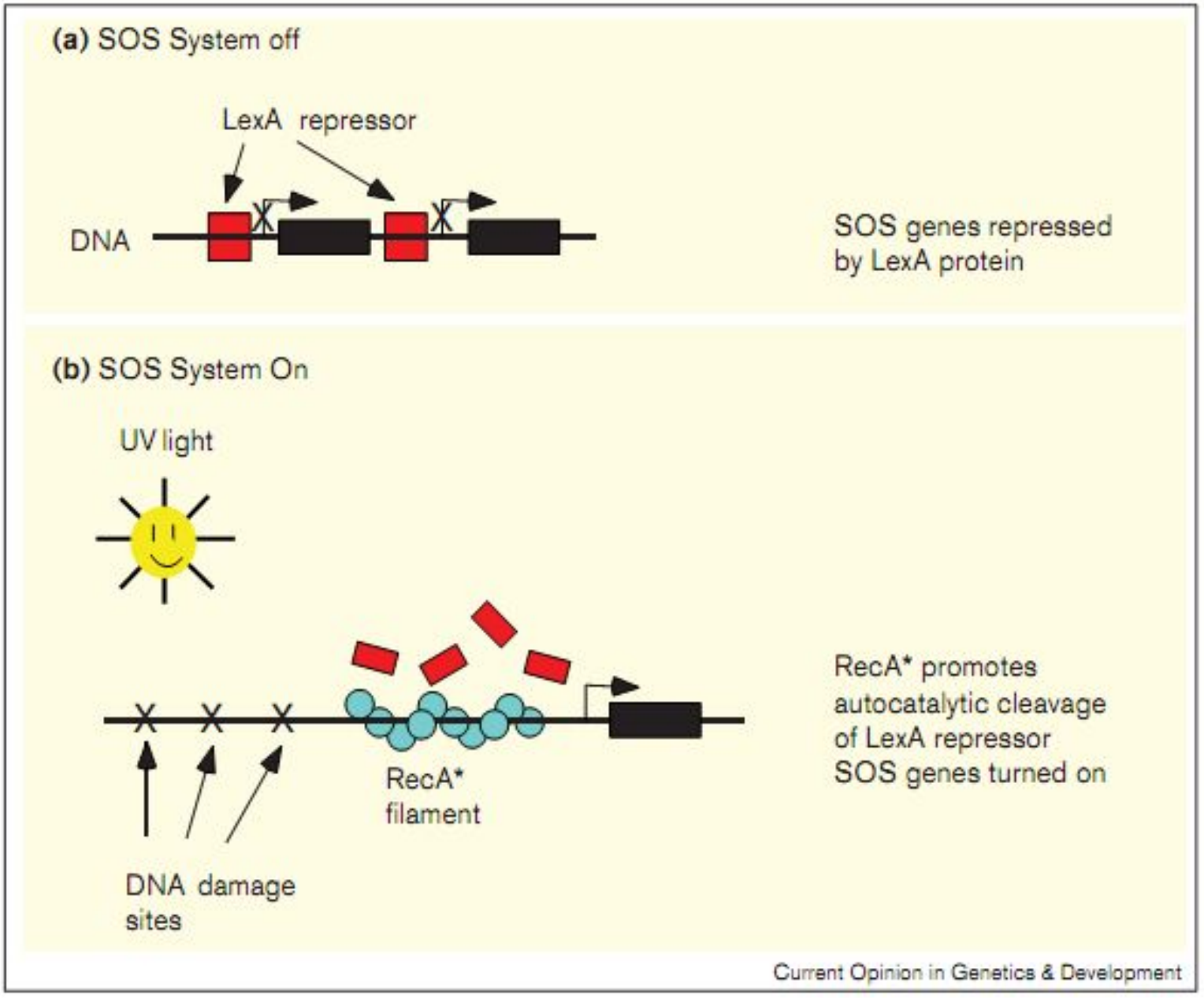
B.

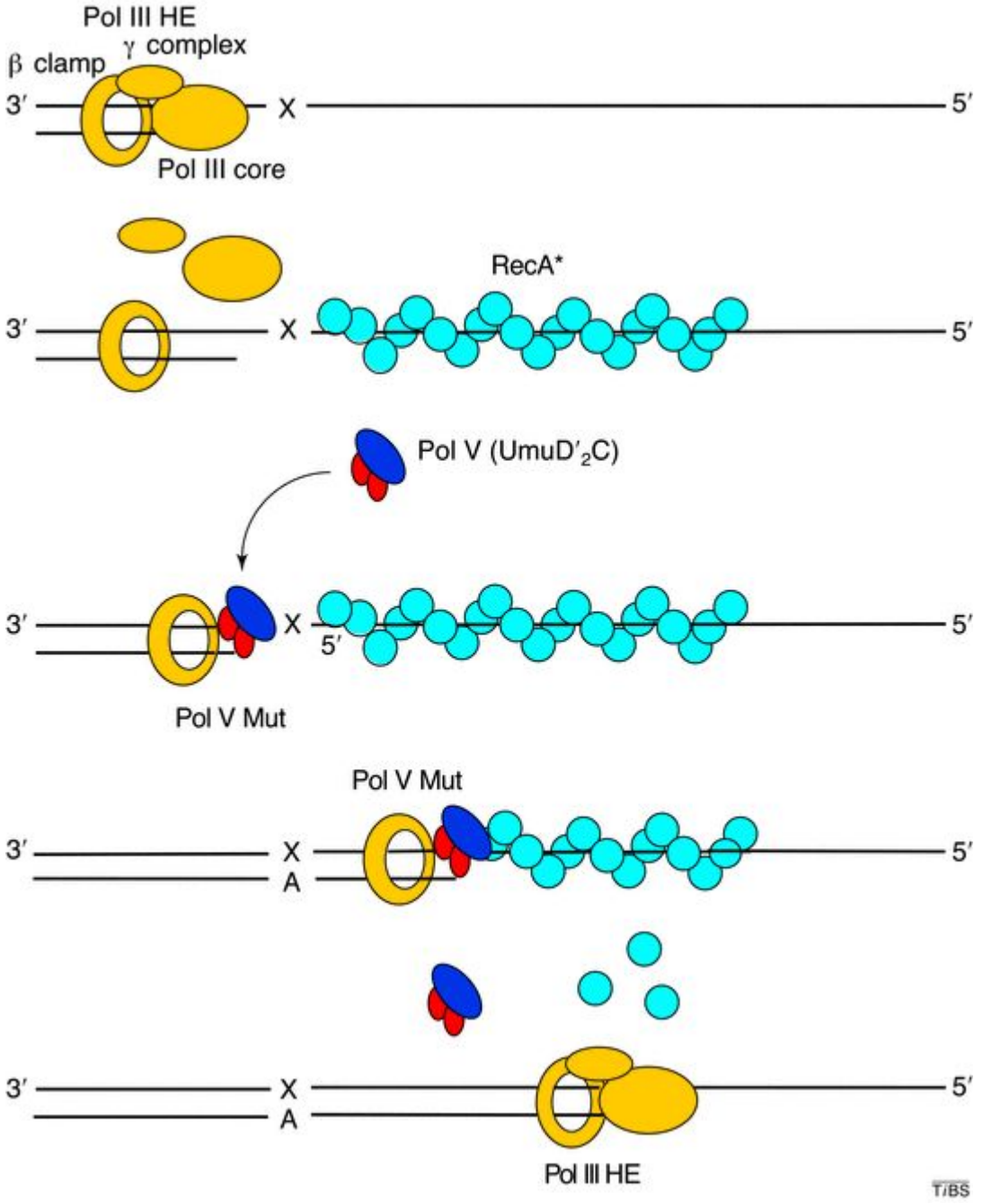

NH2
CH3
dR
1-meA
Fe(II)
AlkB
αKG
O2
CO2
succinate
CH2OH
adenine
HCHO
3-meC
cytosine


NH2
H3C
A
N
H
O
DNA
H2N
C
AlkB
hABH2
hABH3
Formaldehyde
DNA repair
HO
RNA
RNA repair

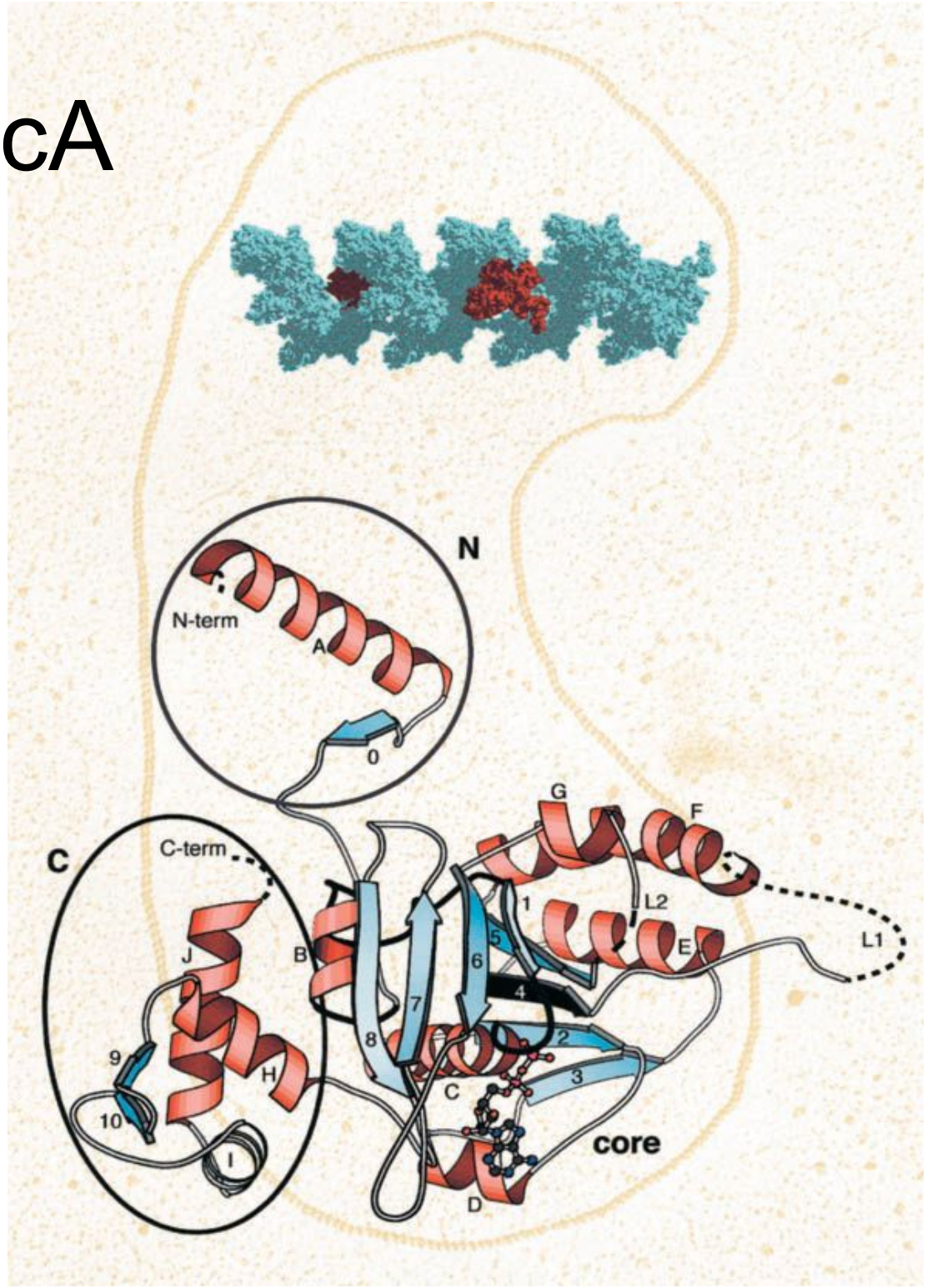

Cytotoxicity
AlkB-homologues
(1-meA, 3meC, others?)
RNA
N-alkylation
1-alkA
3-alkA
7-alkA
3-alkG
7-alkG
3-alkT/U
3-alkC
Alk. agent
AlkB-homologues
(1-meA, 3meC, others?)
DNA
N-alkylation
BER (MPG)
(3-alkA, 7-alkA,
3-alkG, 7-alkG)
AGT
(O6-alkG
>>O4-alkT)
NER
(O4-alkT)
Cytotoxicity
mutations
O6-alkG
O4-alkT
O2-alkT
O2-alkC
O-alkylation
Replication
O6-alkG:T/C
Futile MMR cycle
G*
Single
strand
gap
Replication
Replication
O6-alkG:T/C
A:T
Mutations
Double
strand
break
NHEJ
HR
Cytogenetic
changes
Cell
death

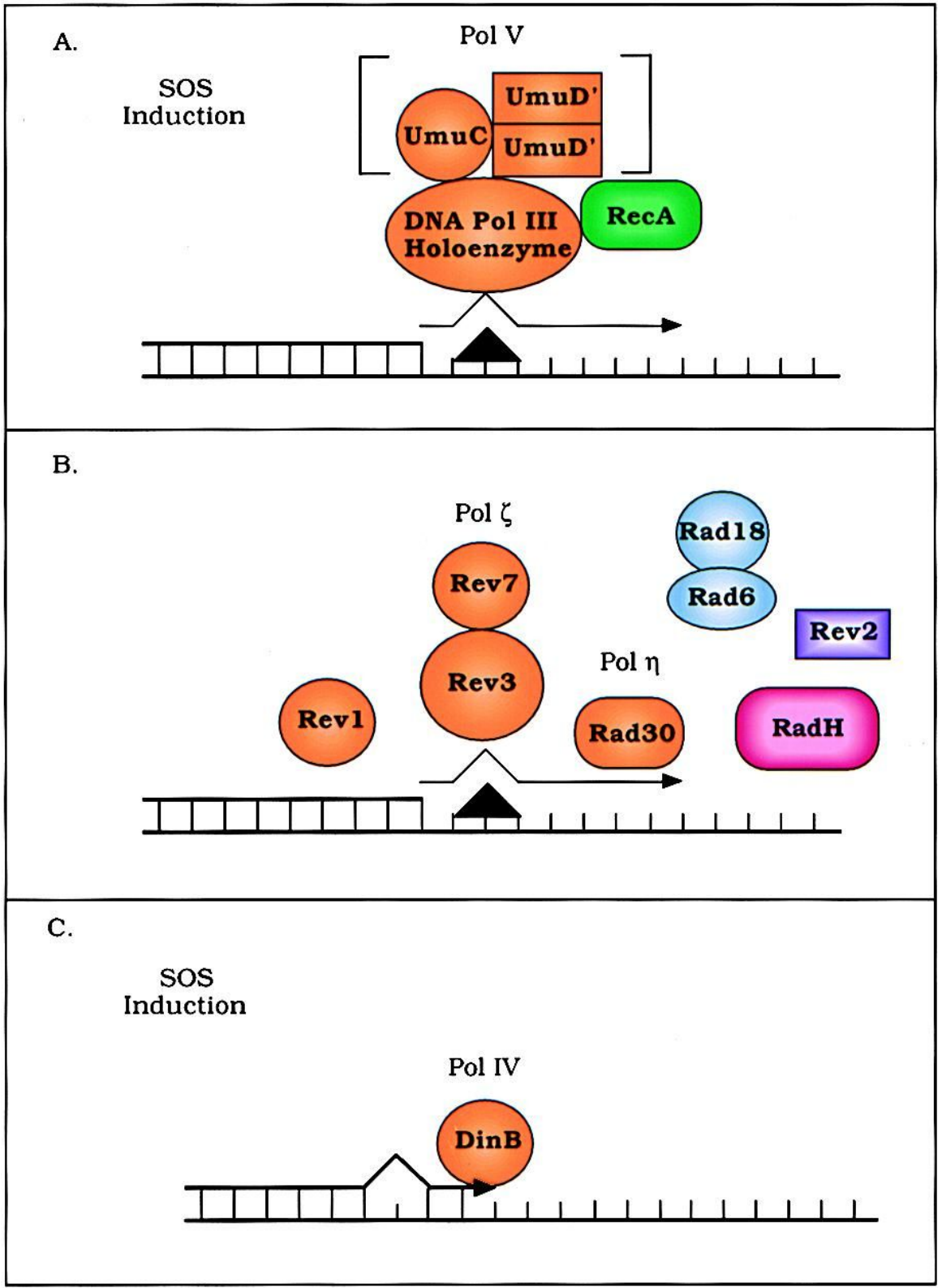
SOS

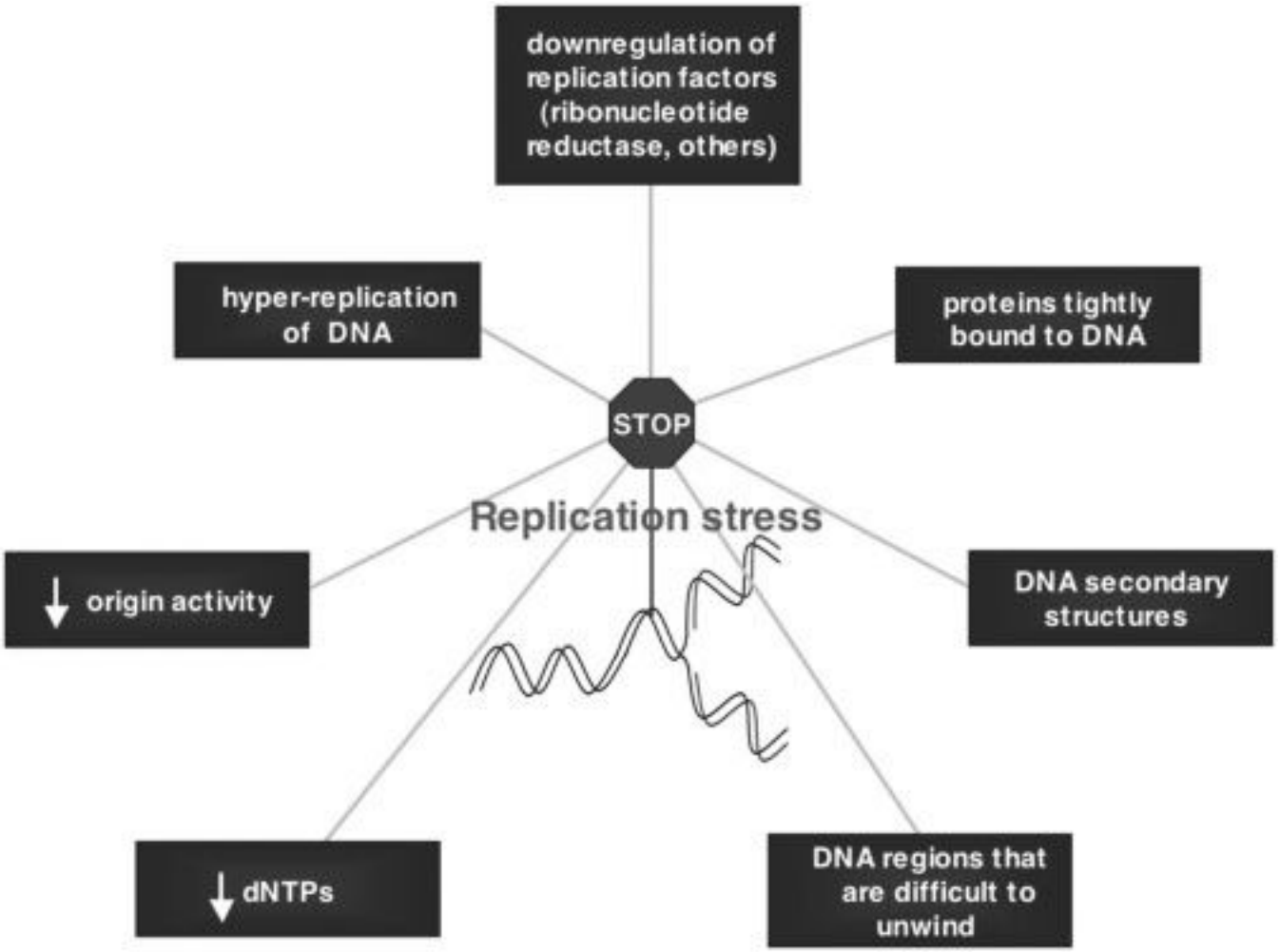

(a) SOS System off
LexA repressor
DNA
SOS genes repressed
by LexA protein
(b) SOS System On
UV light
RecA*
filament
DNA damage
sites
RecA* promotes
autocatalytic cleavage
of LexA repressor
SOS genes turned on
Current Opinion in Genetics & Development

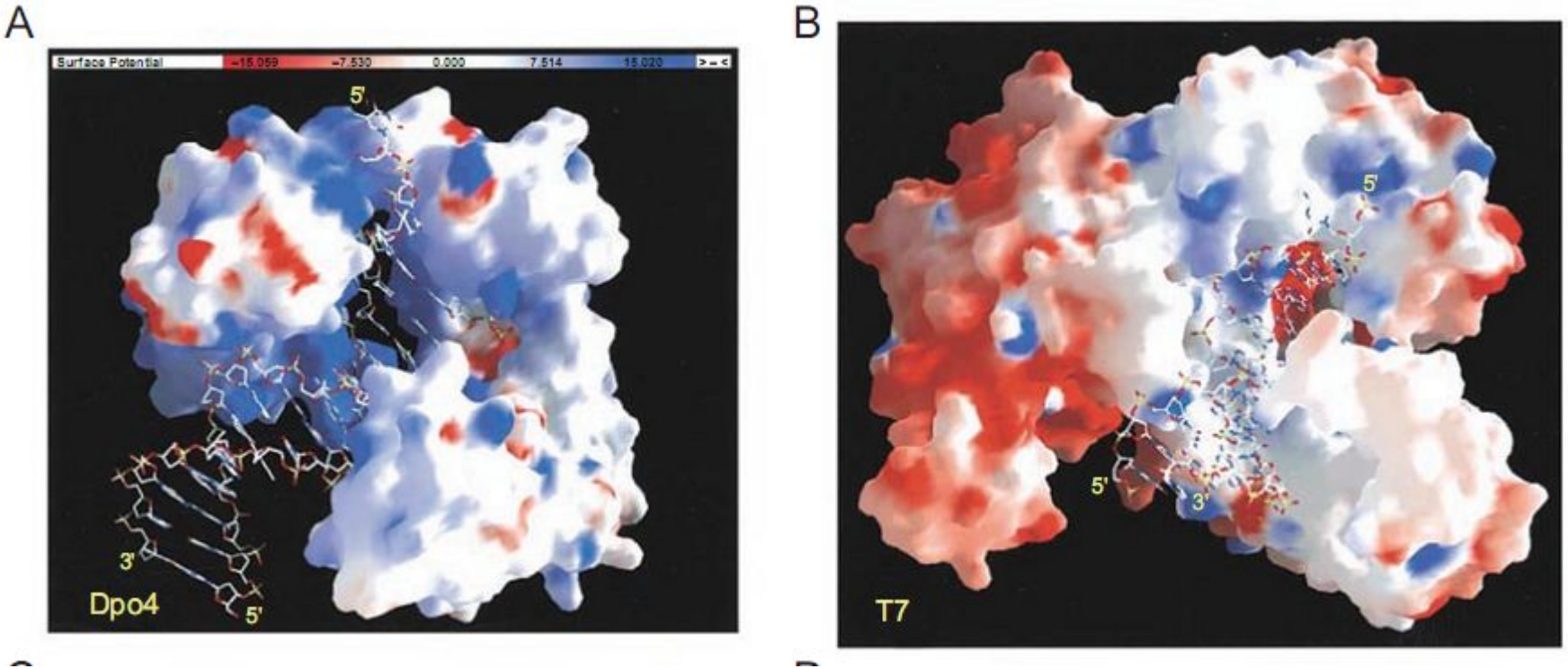

Pol III HE
β clamp
γ complex
3′
X
5′
Pol III core
RecA*
Pol V (UmuD′2C)
5′
Pol V Mut
A
TiBS

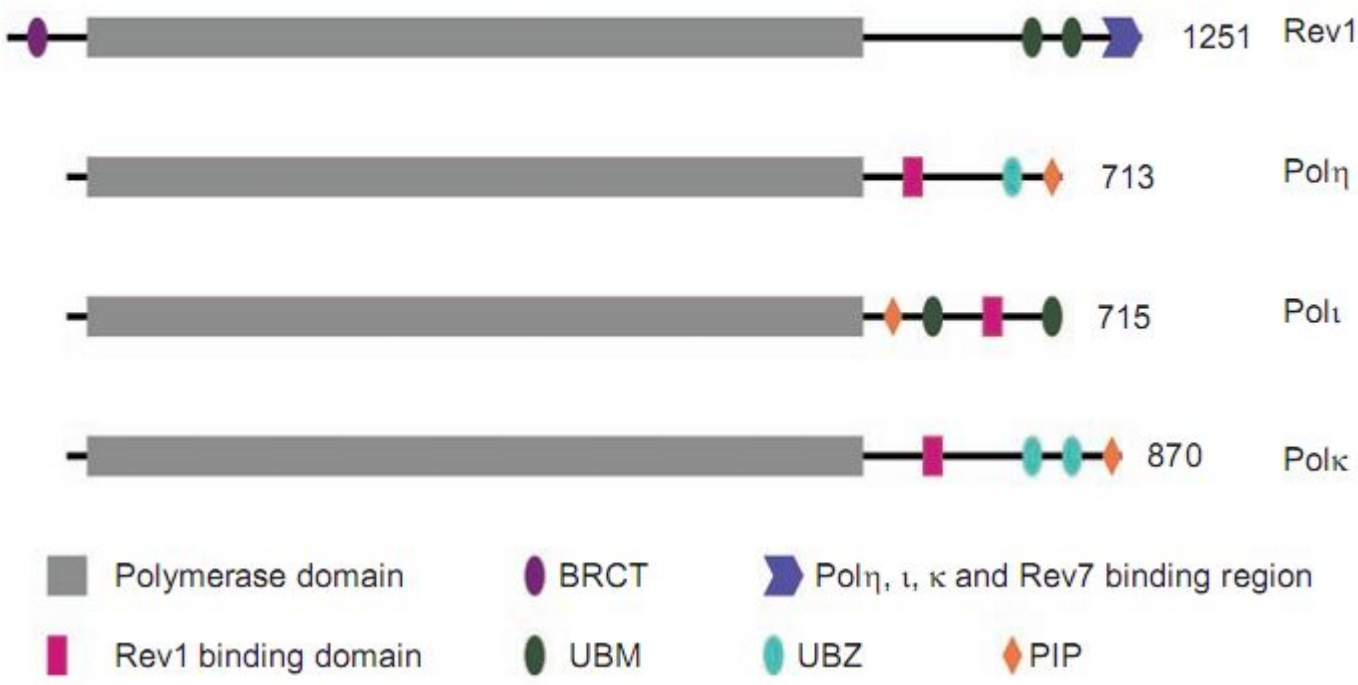
RecA

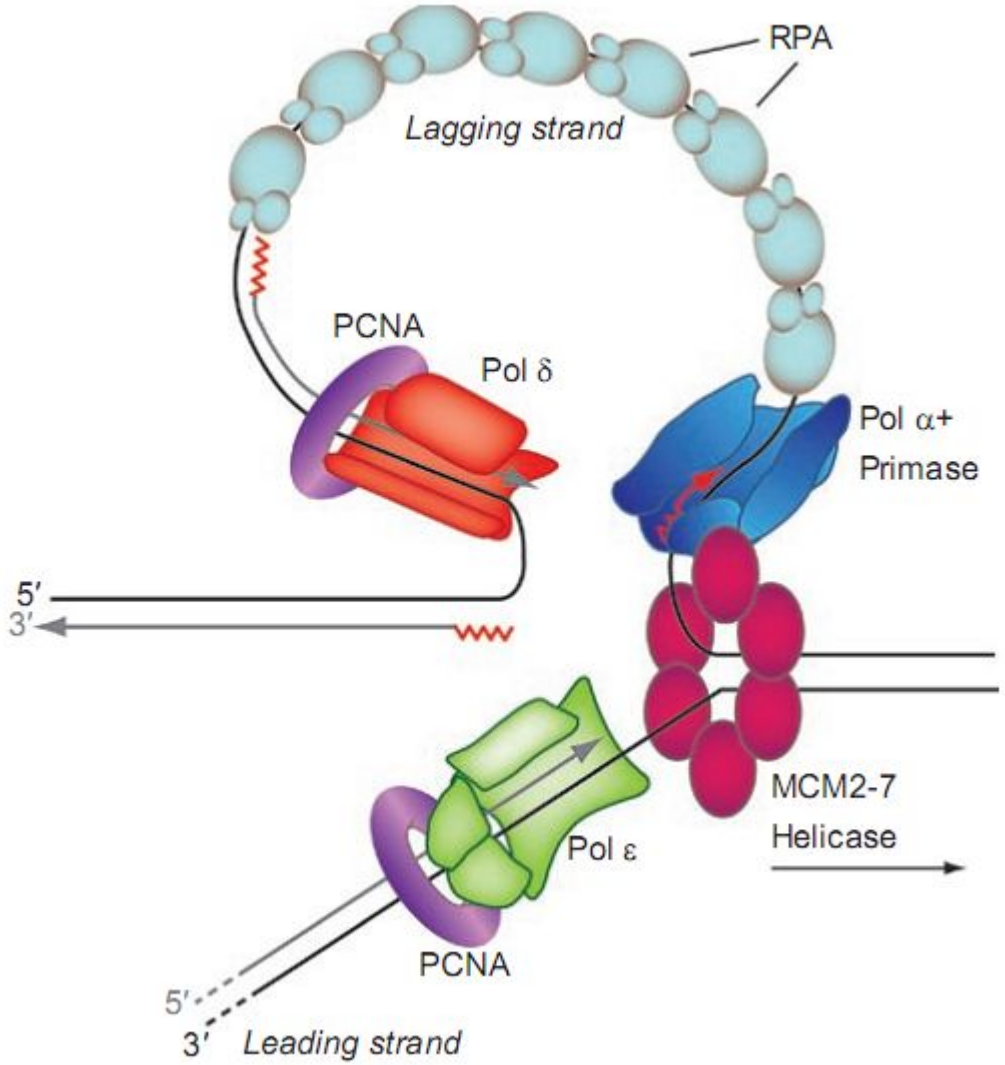


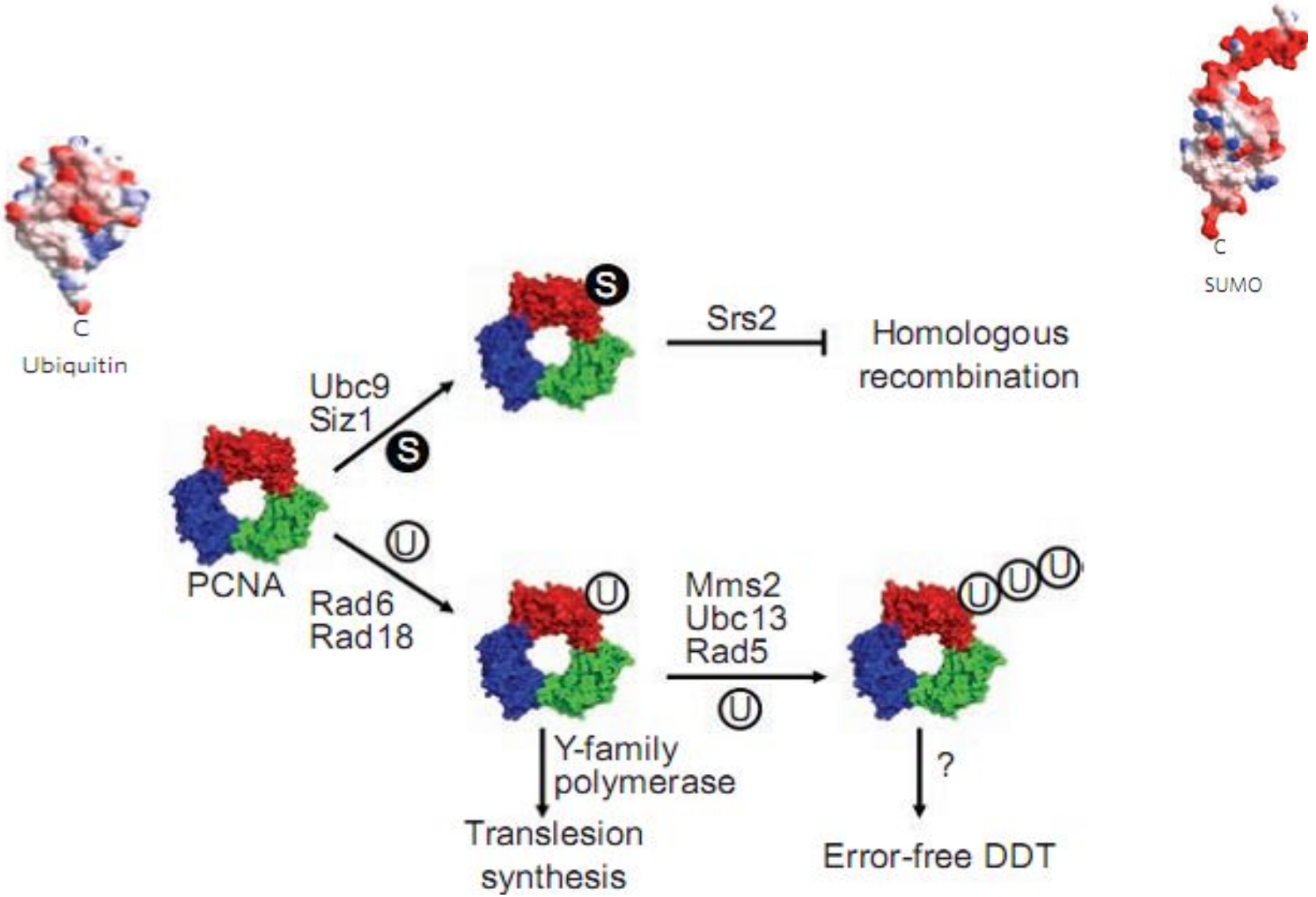

A.
SOS
Induction
Pol V
UmuD'
UmuC
UmuD'
DNA Pol III
Holoenzyme
RecA
B.
Pol ζ
Rev7
Rev3
Rev1
Rad18
Rad6
Rev2
Pol η
Rad30
RadH
C.
SOS
Induction
Pol IV
DinB

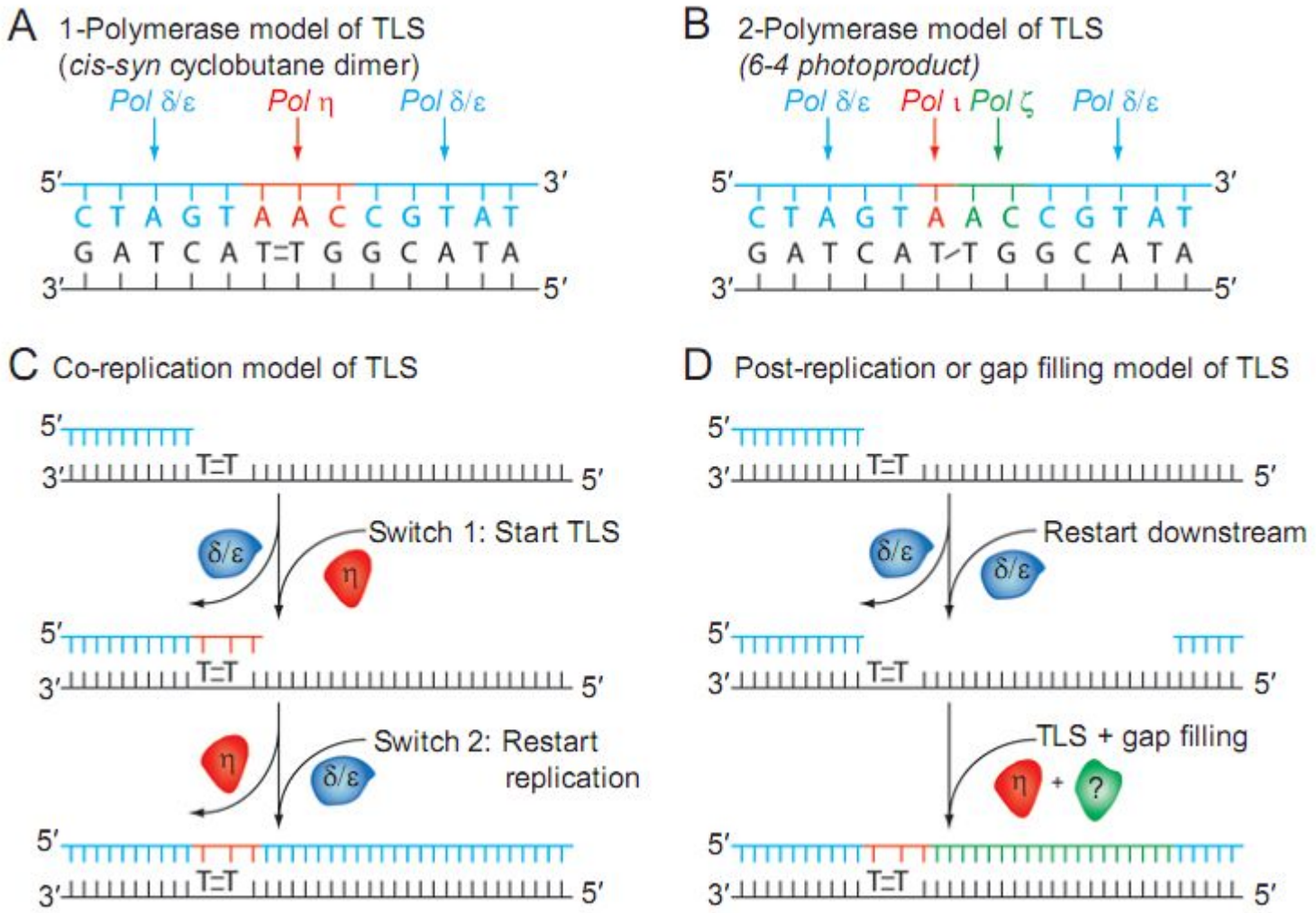

downregulation of replication factors (ribonucleotide reductase, others)
hyper-replication of DNA
proteins tightly bound to DNA
STOP
Replication stress
origin activity
DNA secondary structures
dNTPs
DNA regions that are difficult to unwind

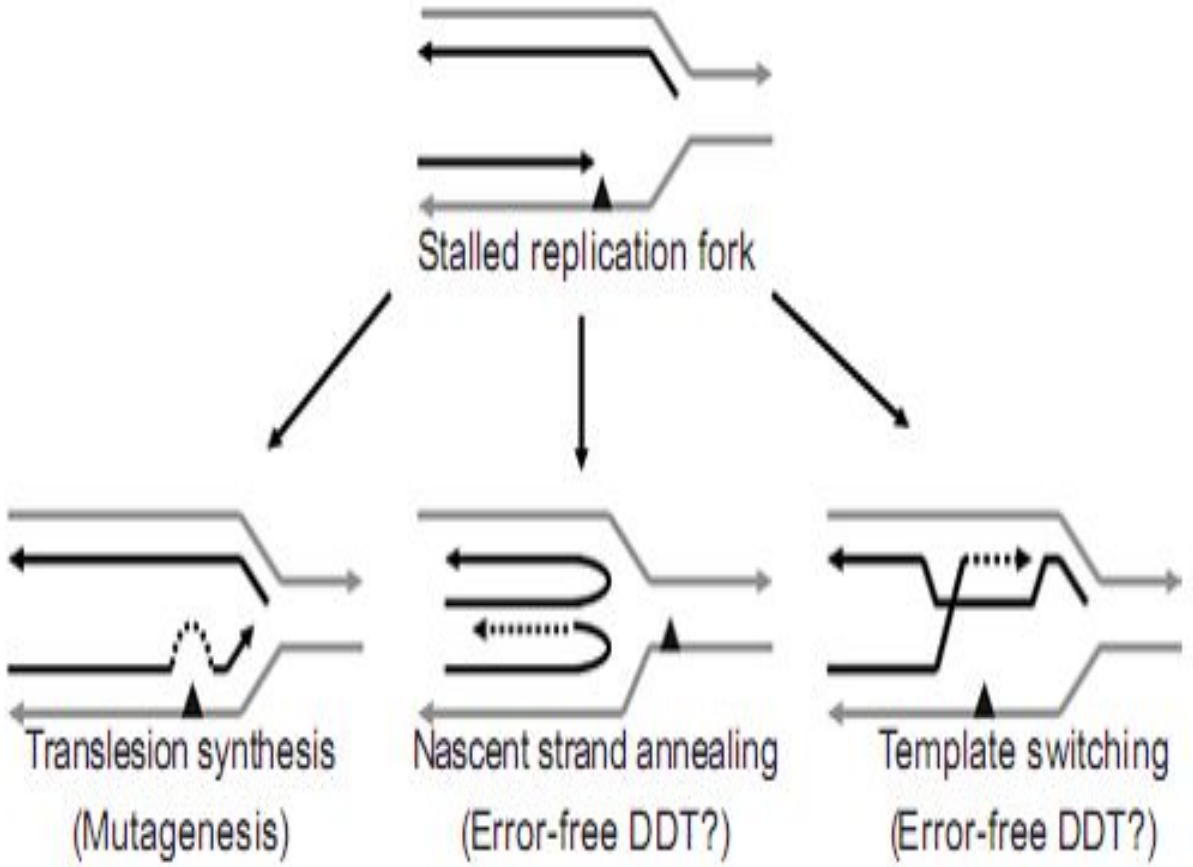

A
Surface Potential
-15.059
-7.530
0.000
7.514
15.029
5'
3'
Dpo4
5'
B
5'
5'
3'
T7


1251
Rev1
713
Polη
715
Polι
870
Polκ
Polymerase domain
BRCT
Polη, ι, κ and Rev7 binding region
Rev1 binding domain
UBM
UBZ
PIP


RPA
Lagging strand
PCNA
Pol δ
Pol α+
Primase
5′
3′
MCM2-7
Helicase
Pol ε
PCNA
5′
3′
Leading strand


C
Ubiquitin
C
SUMO
S
Srs2
Homologous
recombination
Ubc9
Siz1
S
U
PCNA
Rad6
Rad18
U
Mms2
Ubc13
Rad5
U
U U U
Y-family
polymerase
?
Translesion
synthesis
Error-free DDT


A 1-Polymerase model of TLS
(cis-syn cyclobutane dimer)
Pol δ/ε
Pol η
Pol δ/ε
5′
3′
C T A G T A A C C G T A T
G A T C A T=T G G C A T A
3′
5′
B 2-Polymerase model of TLS
(6-4 photoproduct)
Pol δ/ε
Pol ι
Pol ζ
Pol δ/ε
5′
3′
C T A G T A A C C G T A T
G A T C A T–T G G C A T A
3′
5′
C Co-replication model of TLS
5′
3′
T=T
5′
δ/ε
η
Switch 1: Start TLS
5′
3′
T=T
5′
η
δ/ε
Switch 2: Restart
replication
5′
3′
T=T
5′
D Post-replication or gap filling model of TLS
5′
3′
T=T
5′
δ/ε
δ/ε
Restart downstream
5′
3′
T=T
5′
TLS + gap filling
η
+
?
5′
3′
T=T
5′


Stalled replication fork
Translesion synthesis
(Mutagenesis)
Nascent strand annealing
(Error-free DDT?)
Template switching
(Error-free DDT?)