

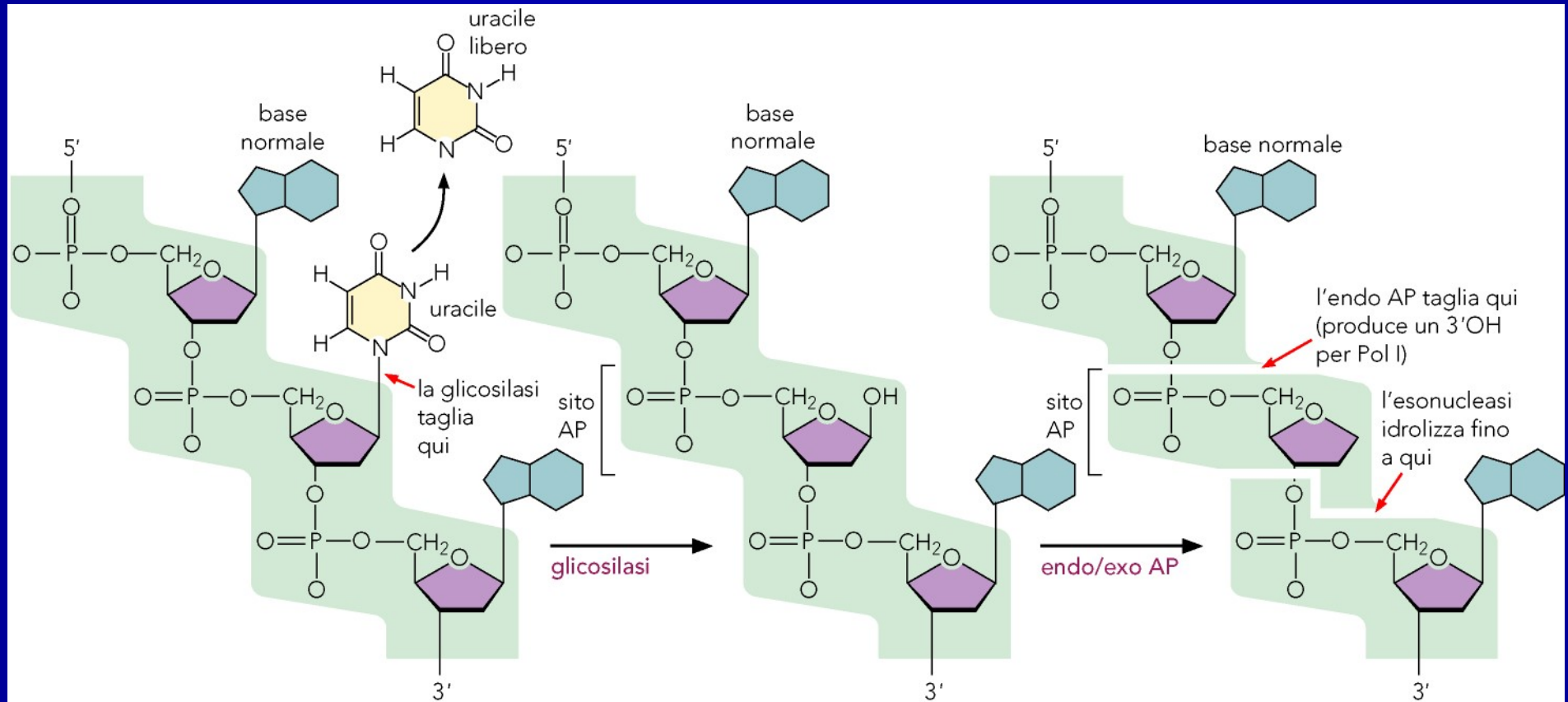
Riparazione per excisione di basi (BER)

Rimuove le basi chimicamente modificate che distorcono localmente la doppia elica

Agisce su danni al DNA piuttosto limitati, quelli che si producono ogni giorno spontaneamente

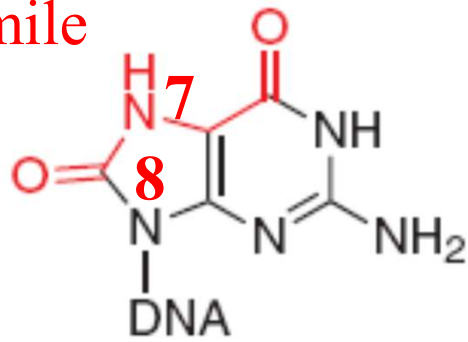
E' il meccanismo prevalente per la rimozione di lesioni che interessano il singolo filamento

Esempio: rimozione uracile dal DNA

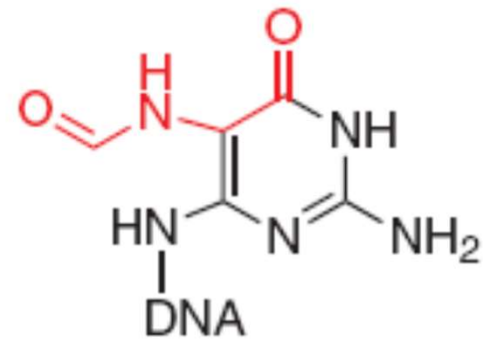


BER: 8-OXOGUANINA

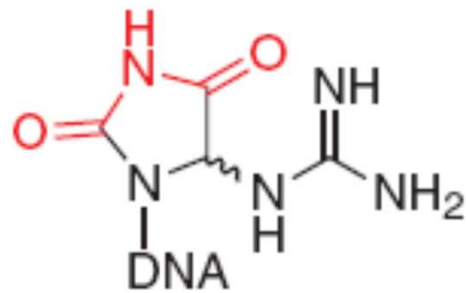
b T simile



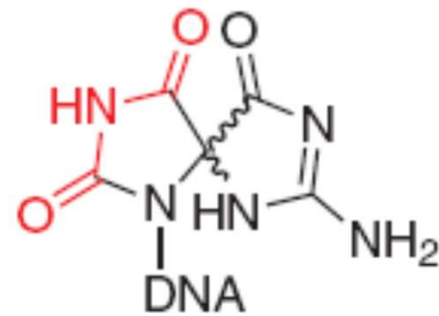
8-oxoG



FapyG

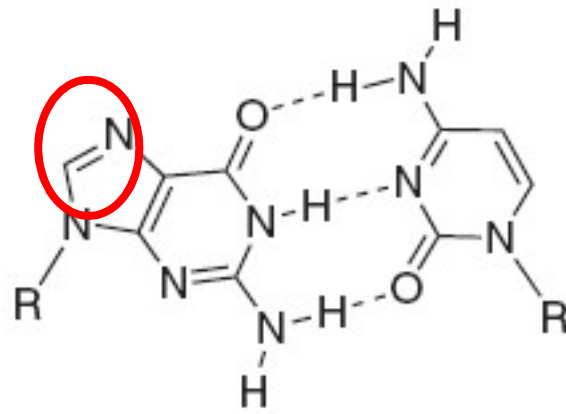


Gh

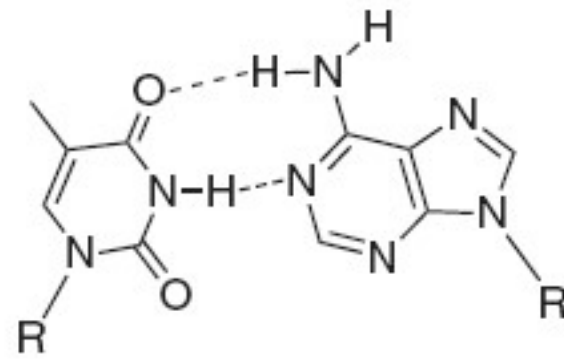


Sp

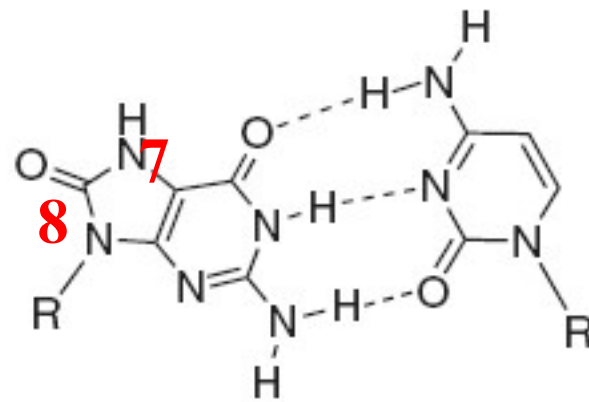
a



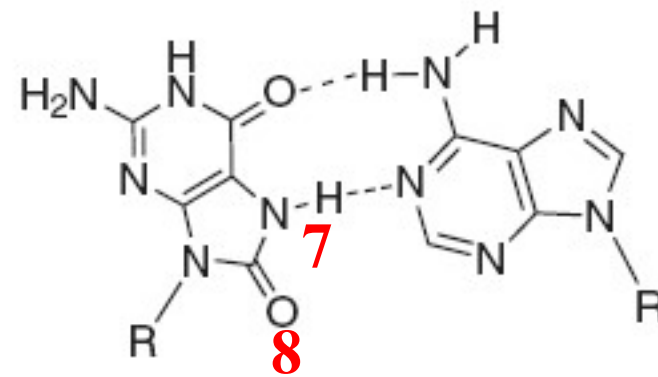
G(anti)•C(anti)



T(anti)•A(anti)



8-oxoG(anti)•C(anti)

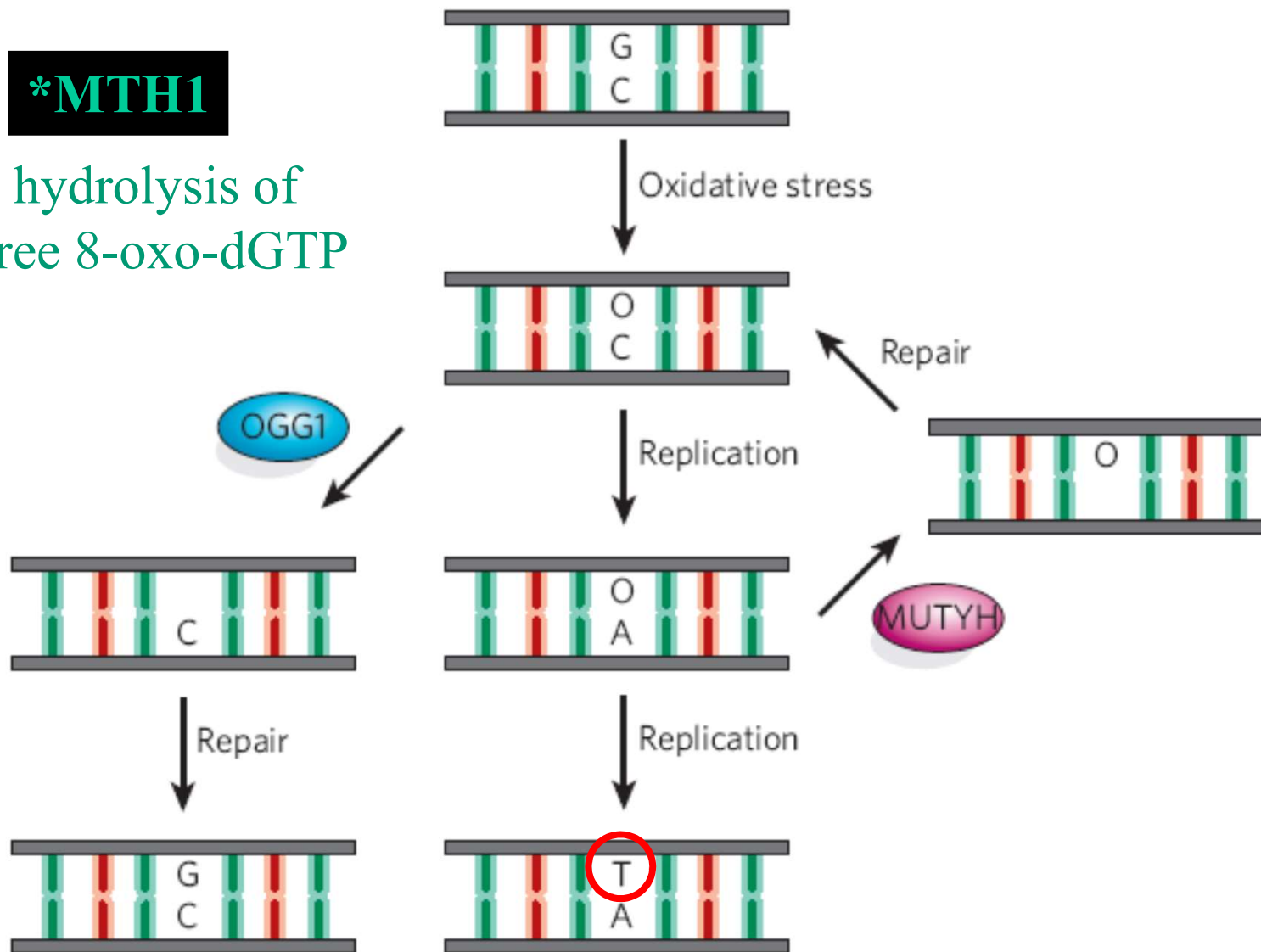


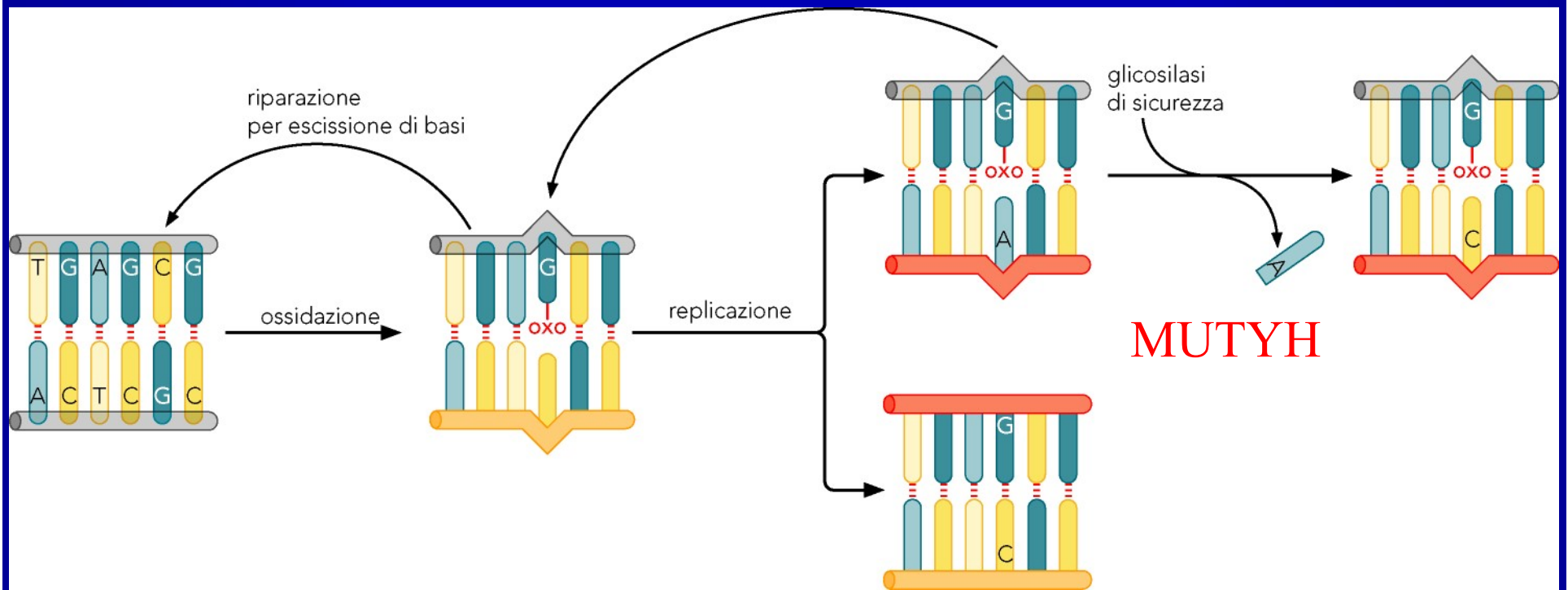
8-oxoG(syn)•A(anti)

- **MutT and its human homologue MTH1 have an important role in preventing the incorporation of 8-oxoG, through hydrolysis of free 8-oxo-dGTP.**

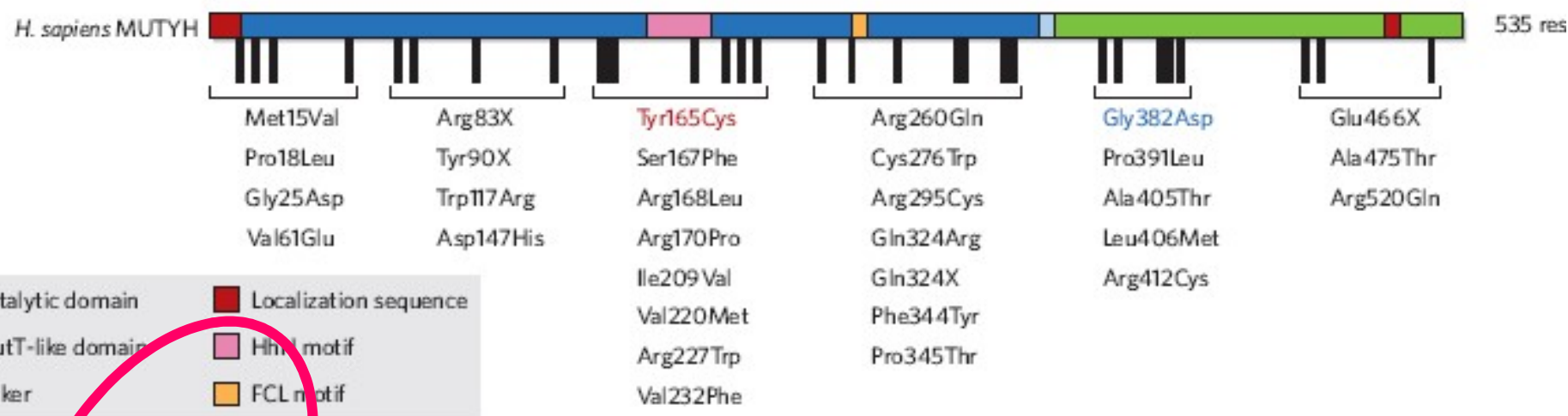
***MTH1**

hydrolysis of
free 8-oxo-dGTP



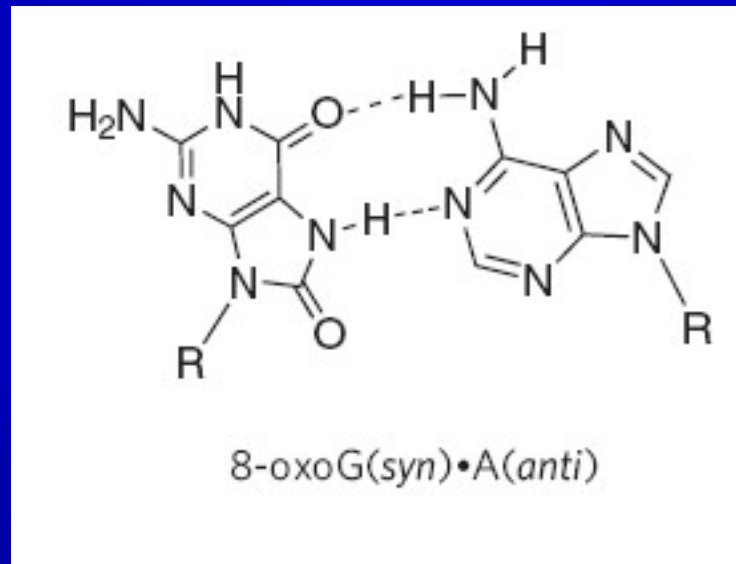


Germline mutations observed in *MUTYH* in individuals with polyposis



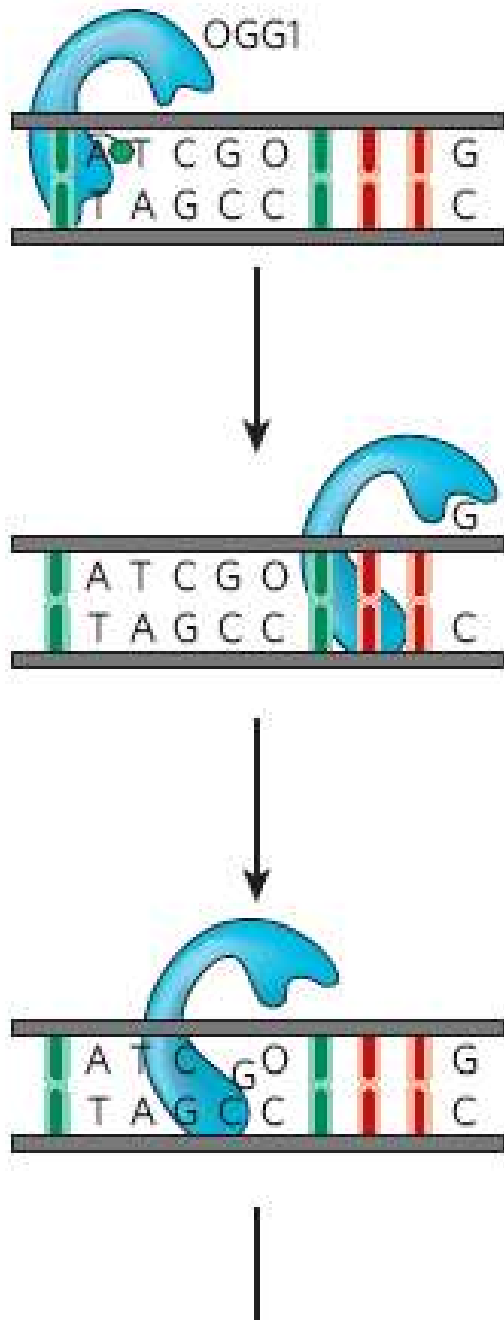
- **DNA-binding motifs: helix–hairpin–helix (HhH) motif and the Fe–S cluster loop (FCL) motif**

- Consistent with a global defect in 8-oxoG•A repair, a high proportion of tumours from patients with biallelic mutations in *MUTYH* have been observed to contain G-to-T transversions



Uomini e Topi....

- mice that are deficient only in MUTYH do not show increased tumorigenesis
- Crossing MUTYH-deficient mice with multiple intestinal neoplasia (*ApcMin/+*) mice
- greater intestinal tumorigenesis than in *ApcMin/+/Mutyh+/+* mice.



The 8-oxoG lesion search process.

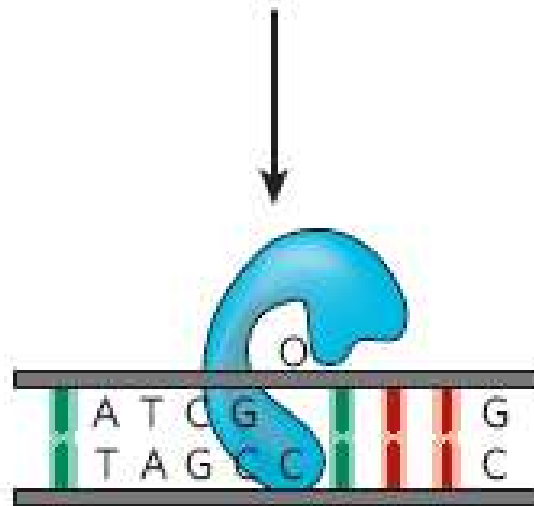
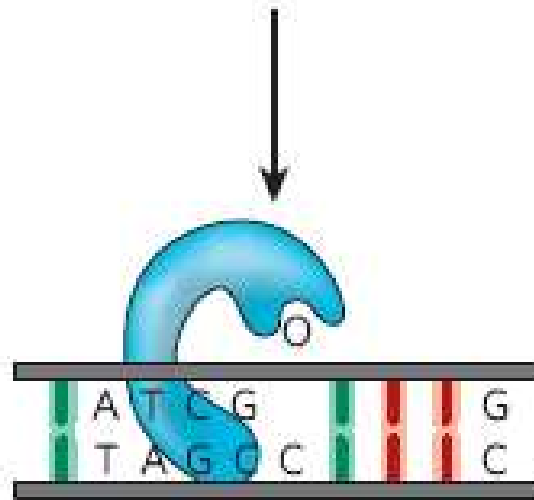
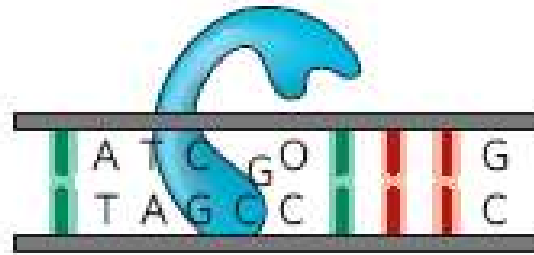
- The enzyme tracks rapidly along DNA, inserting a 'probe' amino-acid residue (green hexagon Phe 114) at various base pairs to test the stability and/or deformability of the duplex.
- OGG1 samples millions of base pairs per second!!!!!!.

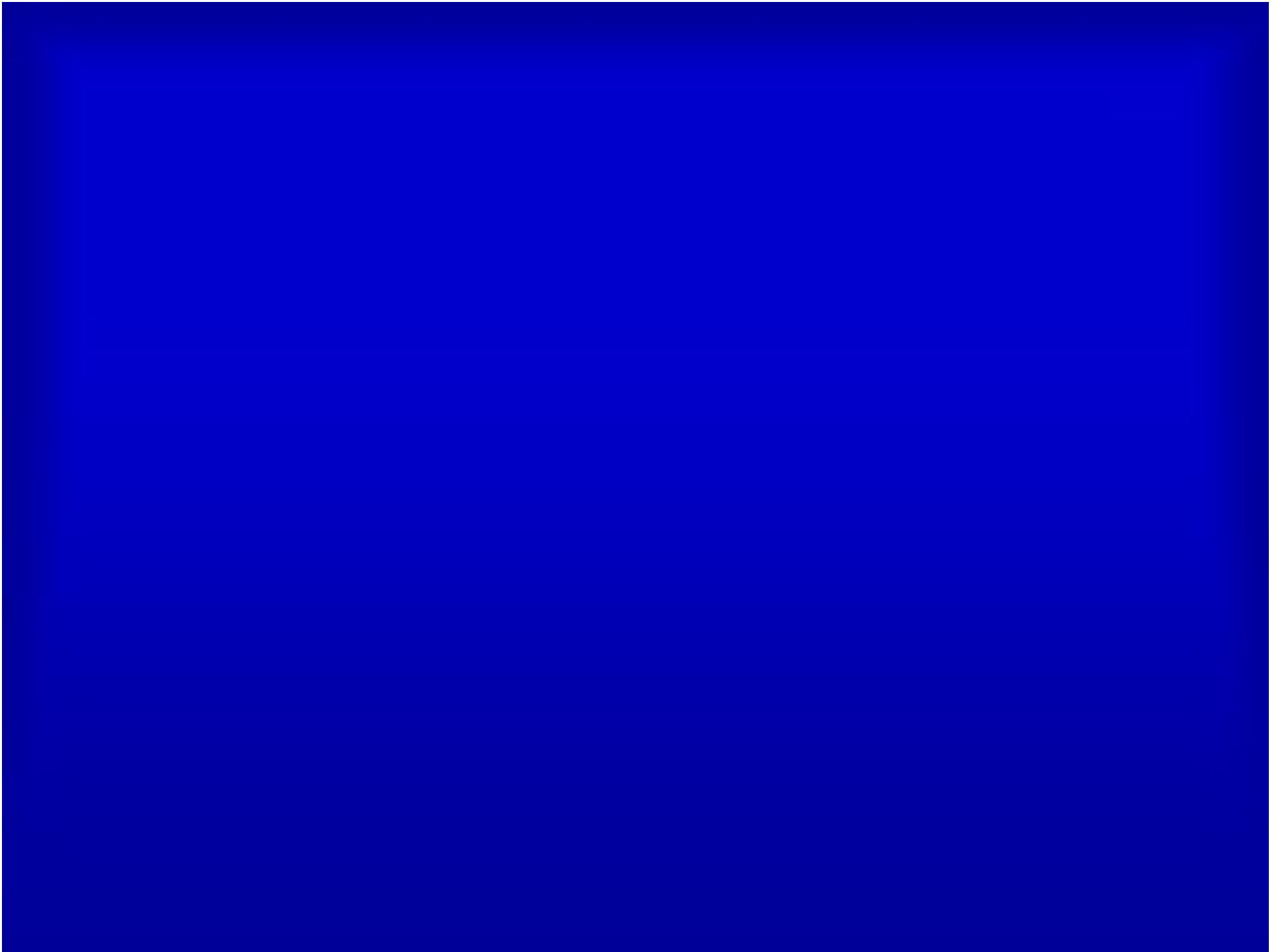
The 8-oxoG lesion search process.

- OGG1 was found to move along the DNA with a diffusion constant approaching the theoretical upper limit for **one-dimensional diffusion** indicating that OGG1 samples millions of base pairs per second.
- the estimated barrier to sliding is extremely small (0.5 kcal mol⁻¹).
- The smaller barrier and the observed unbiased random movement of OGG1 on DNA suggest that OGG1 rapidly searches along DNA as a consequence of brownian motion

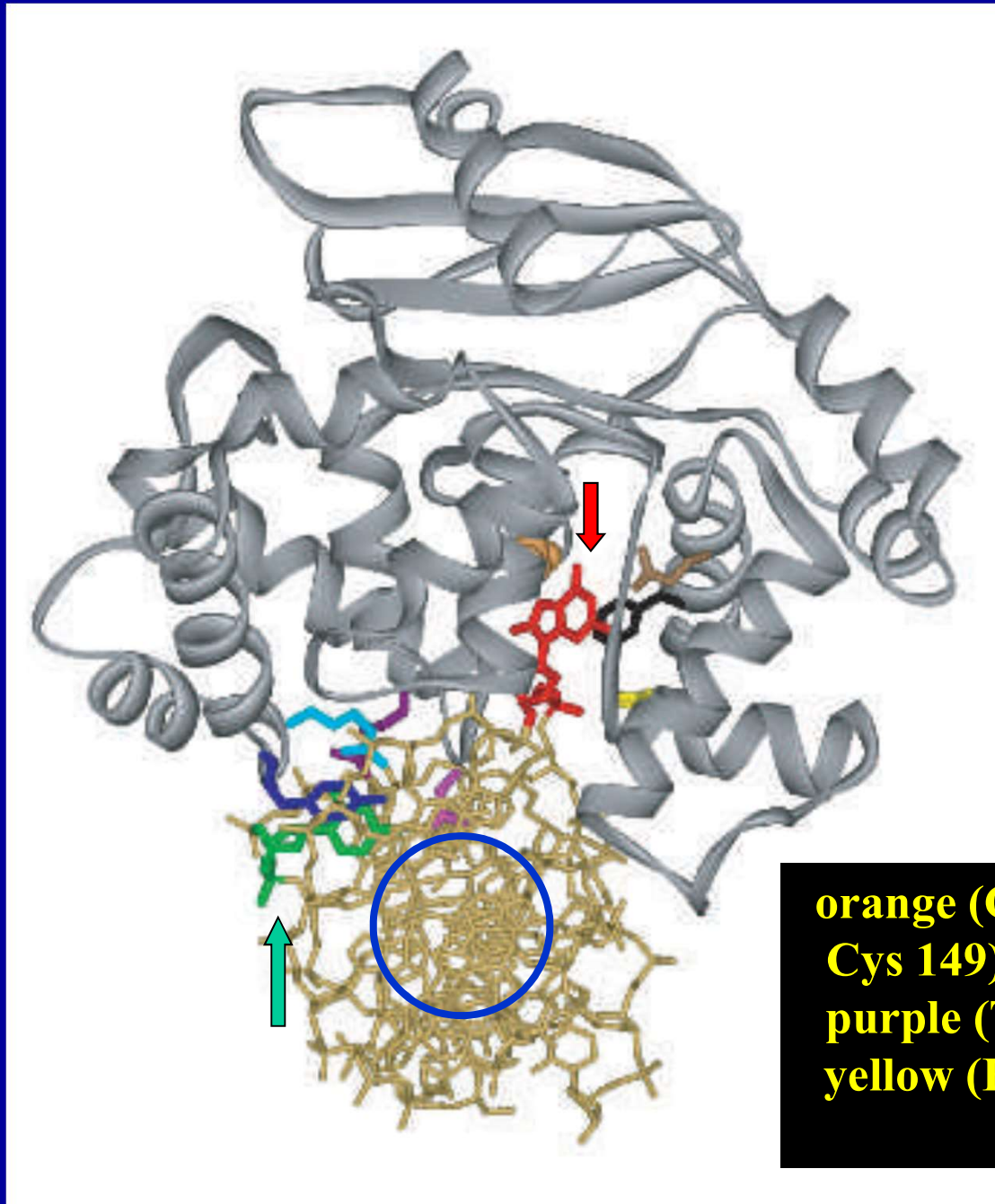
The 8-oxoG lesion search Process (2).

- the 8-oxoG is extruded to the exosite and captured in the 8-oxoG-specific pocket, where it is excised from the DNA.





LRC - Lesion Recognition Complex



**OGG1 LRC with
8-oxoG•C-containing
DNA. 8-oxoG is shown
in red, .**

**and the C
in green**

**orange (Gly 42), dark pink (Asn 149 or
Cys 149), light purple (Arg 154), dark
purple (Tyr 203), light blue (Arg 204),
yellow (His 270), brown (Gln 315) and
black (Phe 319).**

PPartecipano al complesso LRC
molti aminoacidi di di OGG1:

orange (Gly 42)

dark pink (Asn 149 or Cys 149),

light purple (Arg 154),

dark purple (Tyr 203),

light blue (Arg 204),

yellow (His 270),

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black (Phe 319)

lesion-recognition complexes (LRCs).

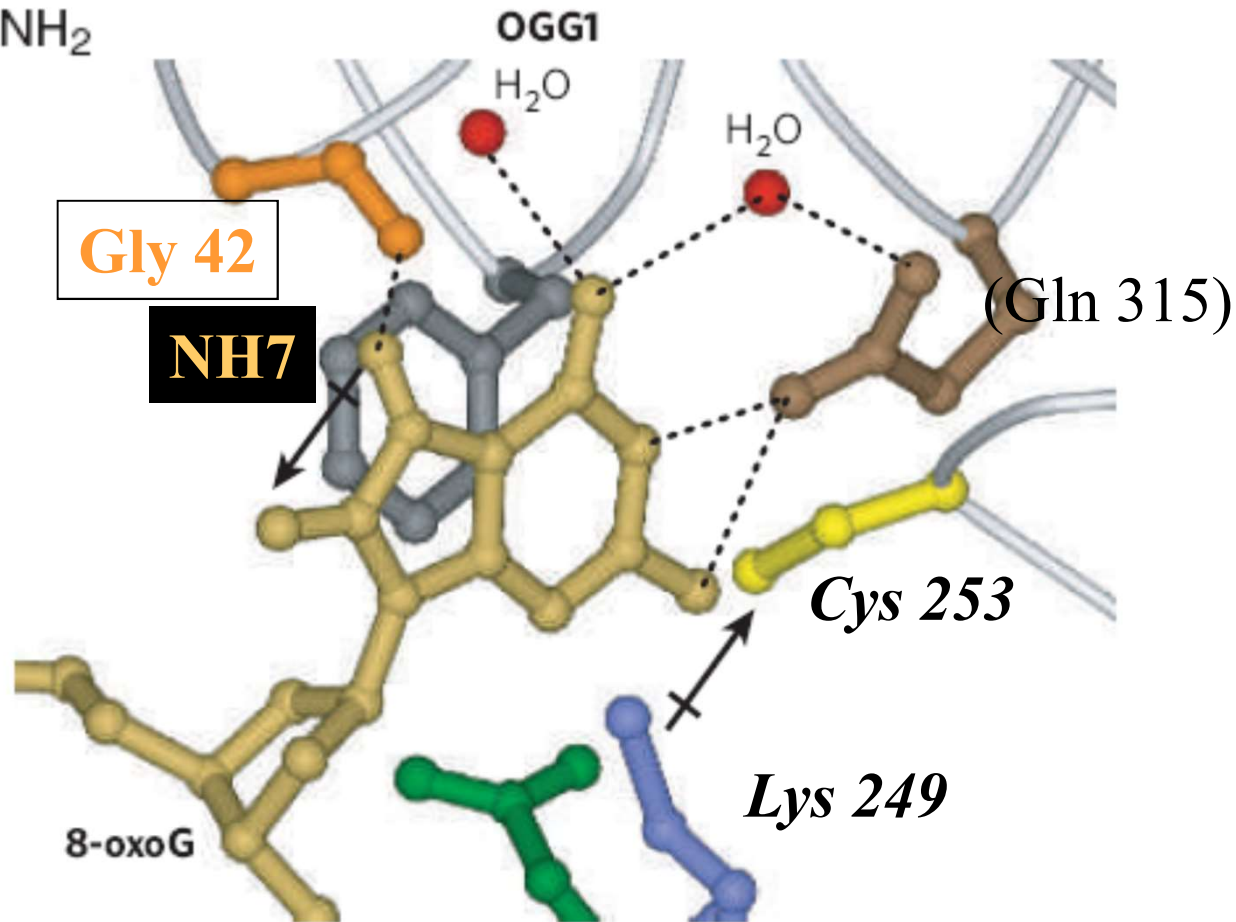
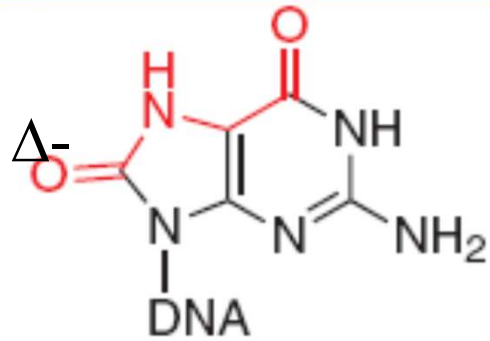


Figure 3 | Recognition of 8-oxoG by OGG1 observed in the LRC of OGG1 with 8-oxoG•C-containing duplexes. This is a view of the base-specific pocket

lesion-recognition complexes (LRCs).

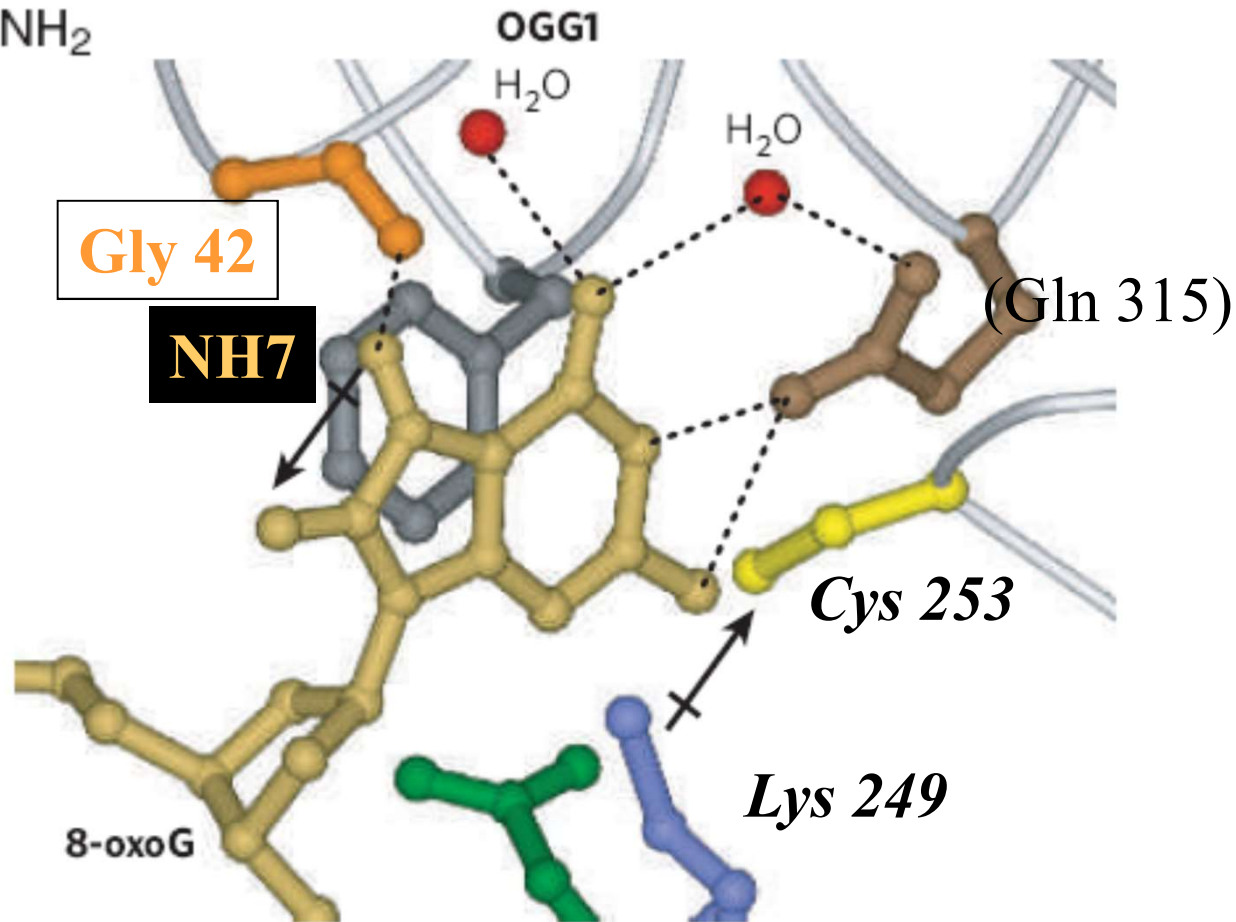
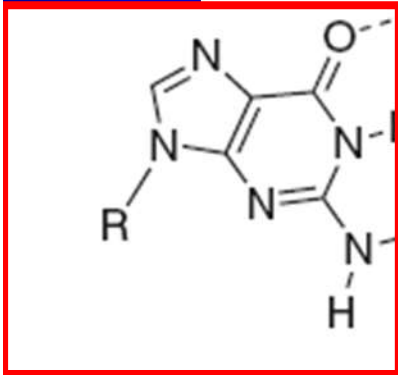
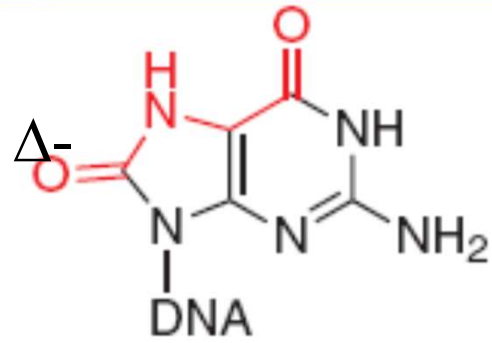


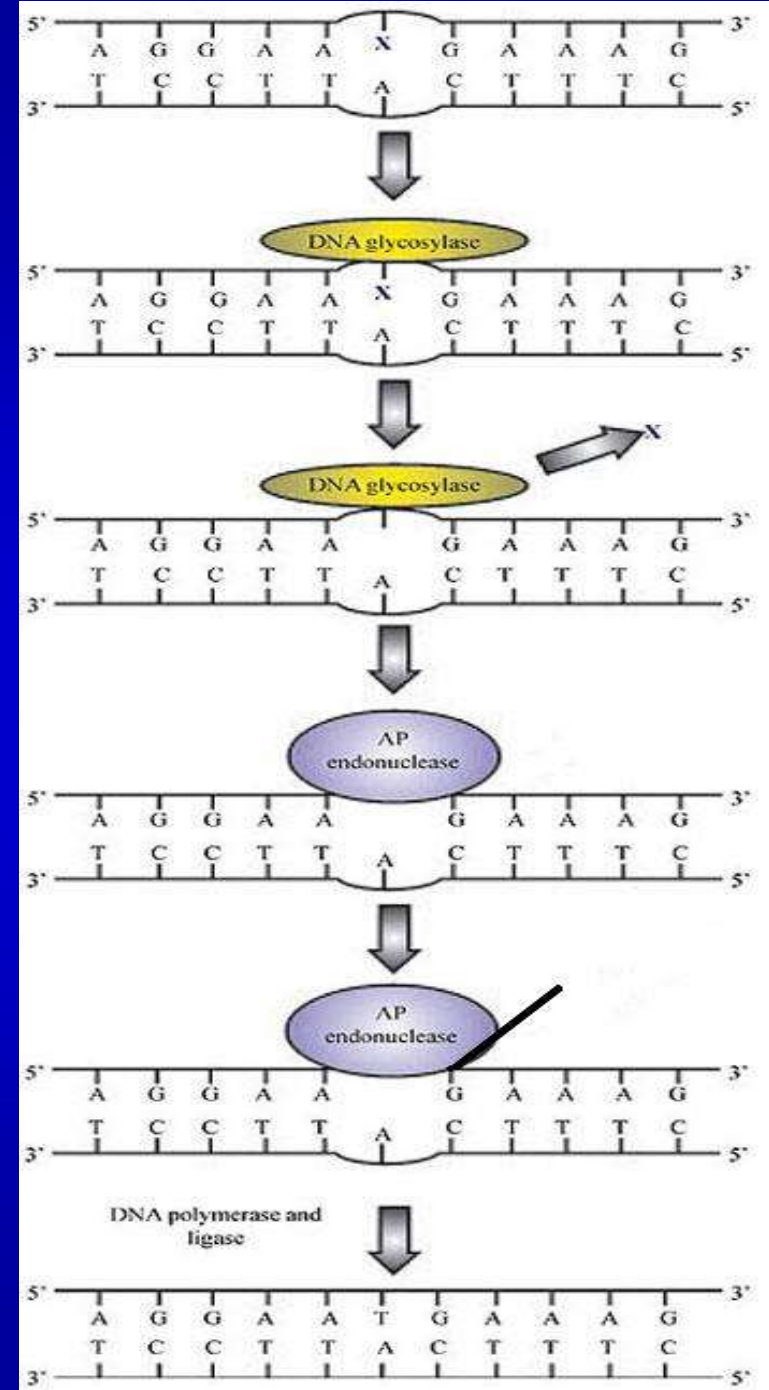
Figure 3 | Recognition of 8-oxoG by OGG1 observed in the LRC of OGG1 with 8-oxoG•C-containing duplexes. This is a view of the base-specific pocket

Una **DNA glicosilasi** (l'uomo ne possiede almeno 8, specifiche per varie lesioni) rompe il legame tra la base errata e il desossiriboso liberando la base

Formazione di un sito AP che viene riconosciuto da **APE1** (AP endonucleasi) → APE1 taglia il singolo filamento in 5' al sito AP

La **DNA polimerasi** riempie il gap lasciato dalla glicosilasi usando come stampo l'elica parentale

La **ligasi** richiude l'elica riparata



OXOGUANINA/BER e
INFIAMMAZIONE/
TRASCRIZIONE

OGG1 and Disease

MEN Adverse deleterious health effects are associated with the diminution of OGG1 activity (population-specific polymorphic variants)

MICE1 Complete loss of OGG1 in murine models displays diet- and age-related induction of metabolic syndrome, highlighting a key role for OGG1 in protecting against these phenotypes.

MICE2 Murine models having enhanced global expression of a mitochondrial-targeted OGG1 demonstrate that they are highly resistant to diet-induced disease.

These data suggest strategies for therapeutic interventions

DNA Repair 2019 Sep;81:102667.

OXOGUANINA e TRASCRIZIONE

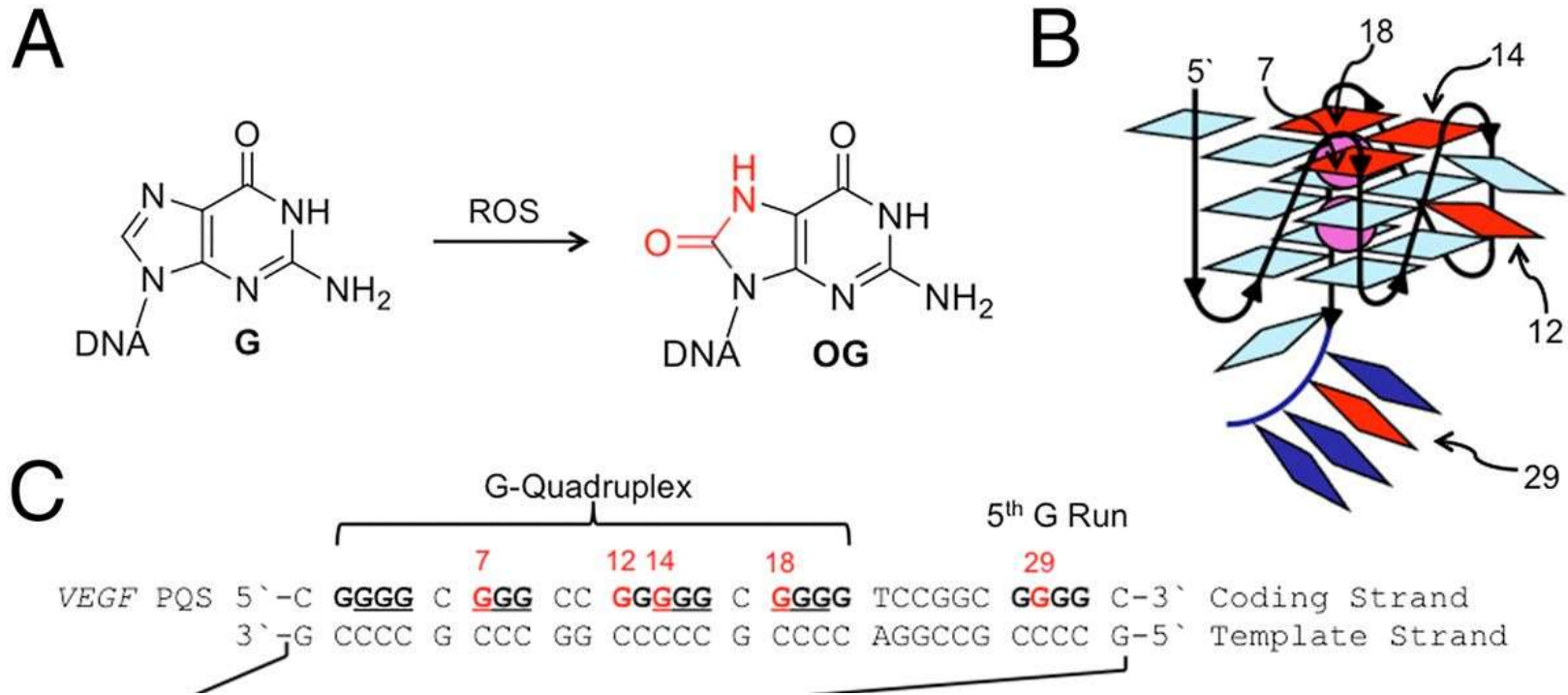
8-oxoguanine (8-oxoG), one of the most abundant genomic base modifications generated by reactive oxygen and nitrogen species, and 8-oxoguanine DNA glycosylase1 (OGG1) have **roles**

- 1** in gene expression through transcription modulation or
- 2** signal transduction.

OXOGUANINA e TRASCRIZIONE 1

Binding to 8-oxoG located in gene regulatory regions, **OGG1 acts as a transcription modulator**, transcription factor homing, induce allosteric transition of G-quadruplex structure, or recruit chromatin remodelers.

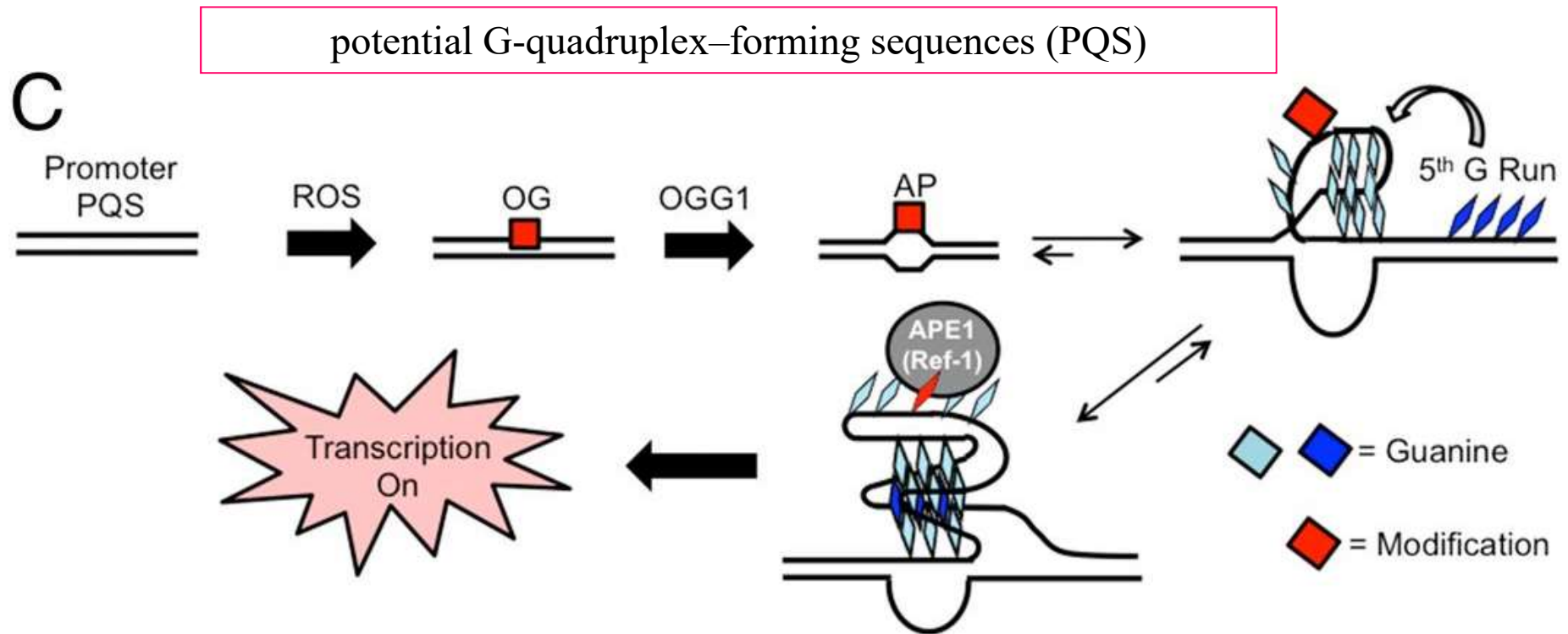
Oxidation of G in the VEGF PQS induces transcription.



potential G-quadruplex-forming sequences (PQS)

Aaron M. Fleming et al. PNAS 2017;114:2604-2609

8-OxoG represents an epigenetic modification

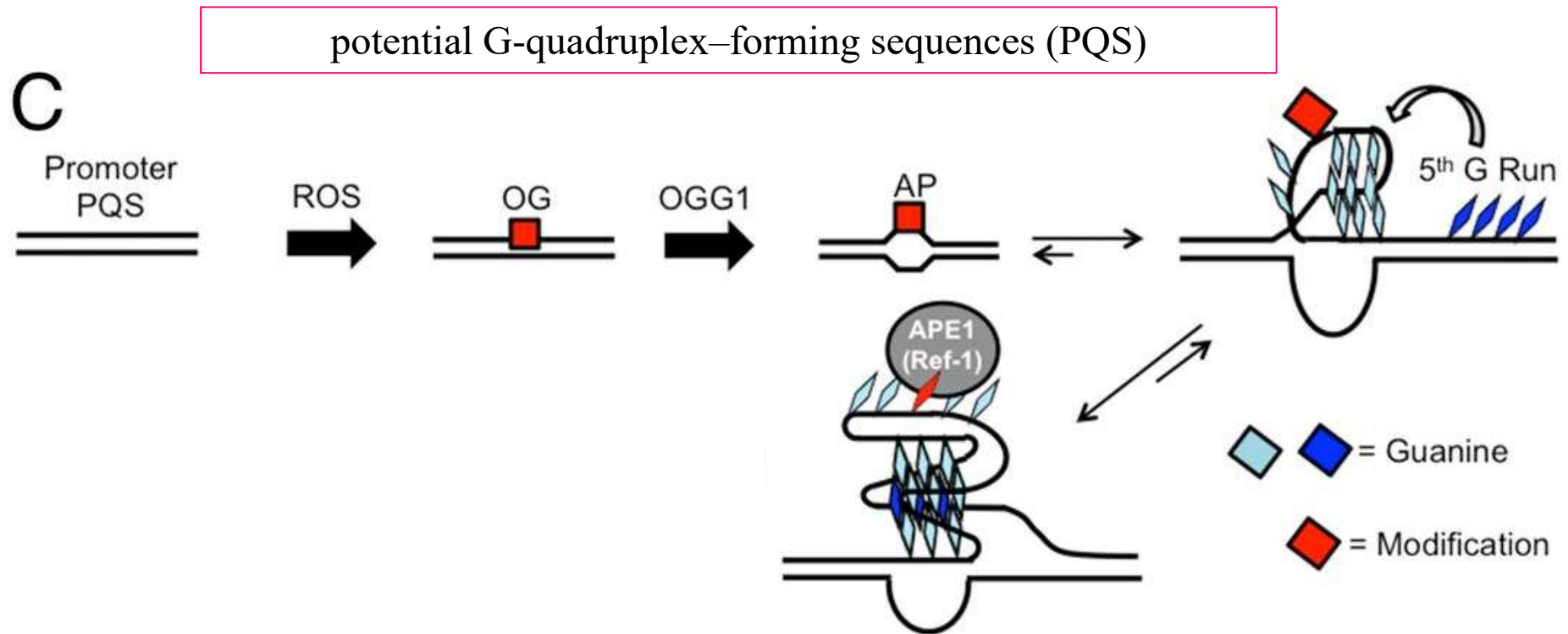


apurinic/apyrimidinic endonuclease 1 (APE1)

initiation of OG removal in the VEGF promoter PQS induces binding of APE1 and activation of transcription (MODEL)

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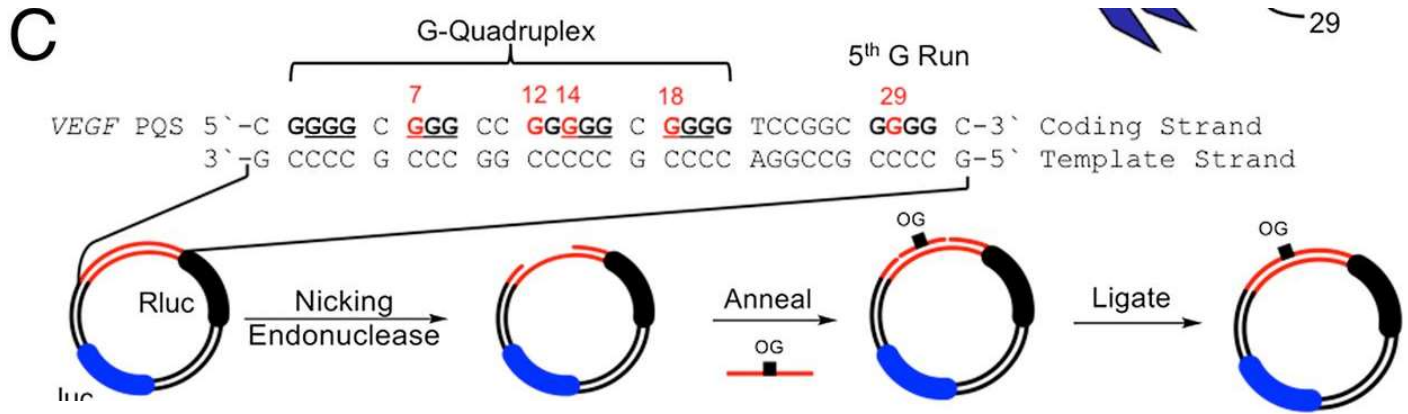
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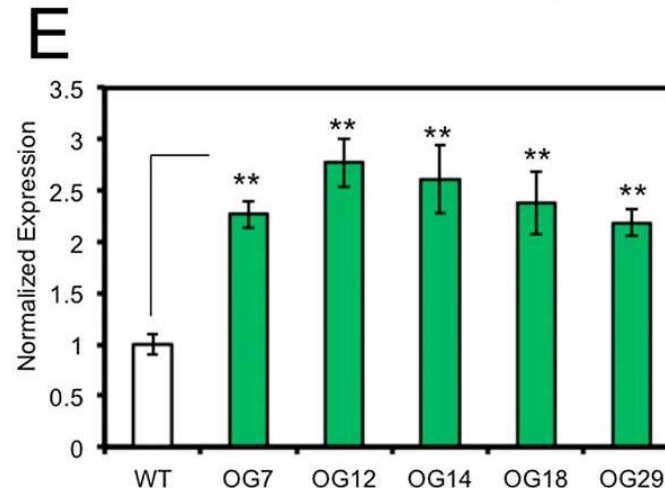
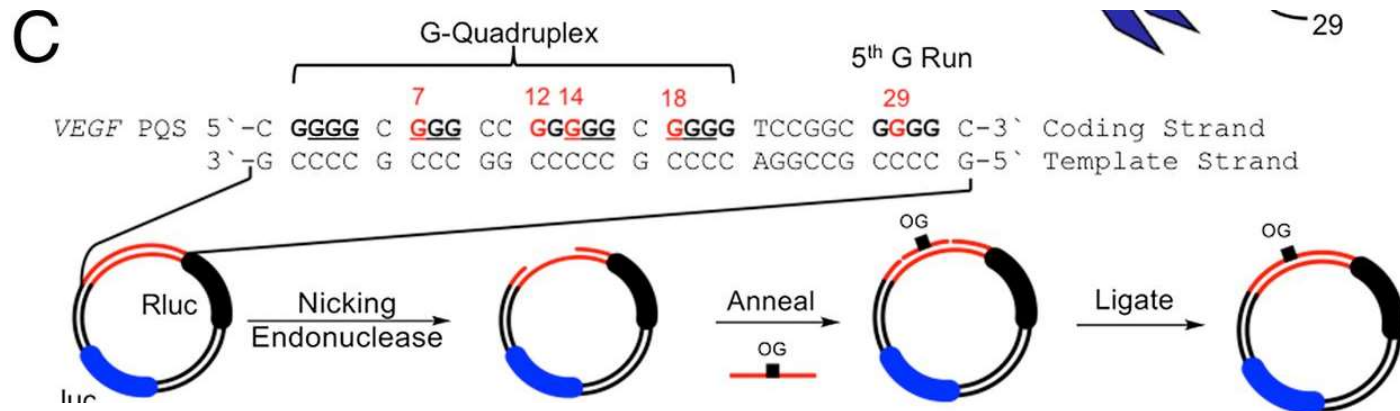
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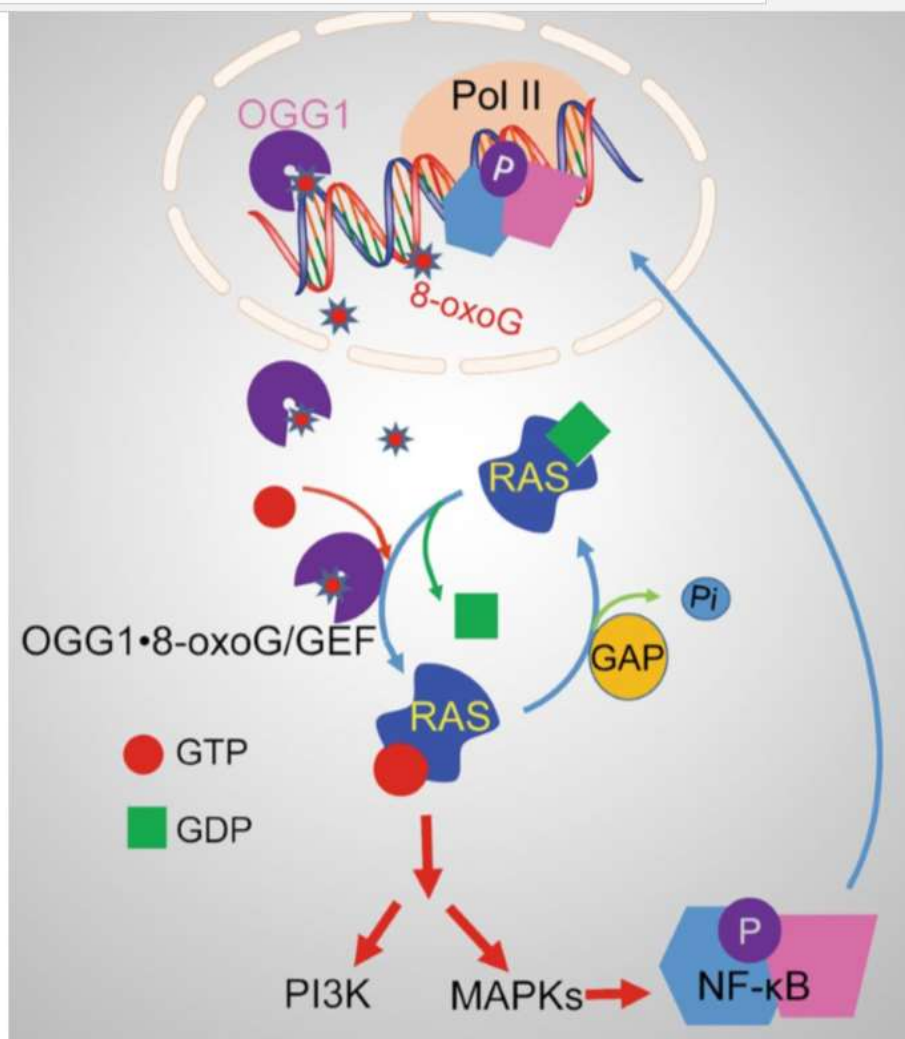
expression at 48 h posttransfection of OG-containing reporters in glioblastoma cells. WT plasmid with the VEGF PQS with undamaged Gs

Aaron M. Fleming et al. PNAS 2017;114:2604-2609

PNAS

OXOGUANINA e TRASCRIZIONE 2

Post-repair complex between OGG1 and its repair product-free 8-oxoG increases the levels of active small GTPases and induces downstream signaling cascades to trigger gene expressions.



8-oxoG-induced conformational change in OGG1 allows its interaction with small GTPases

OGG1·8-oxoG complex causes replacement of GDP with GTP

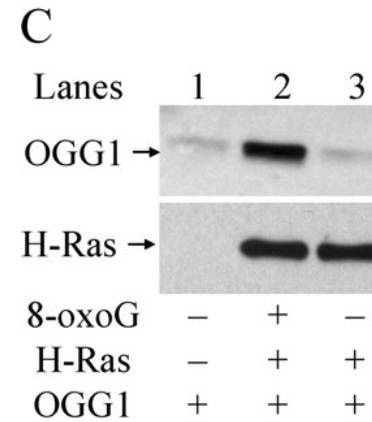
OGG1·8-oxoG also catalyzes the GTP → GDP release “allows rebinding”

OGG1·8-oxoG functions as a guanine-nucleotide exchange factor (GEF).

**OGG1 complexed with 8-oxoG
has guanine nucleotide exchange factor
activity.**

interaction of OGG1 with Ras protein requires 8-oxoG

H-Ras (2.7 pmol) was bound to nickel-agarose beads and OGG1 \pm 8-oxoG was added. After washing the amount of OGG1 bound was analyzed by immunoblotting



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exchange of Ras-bound GDP for GTP

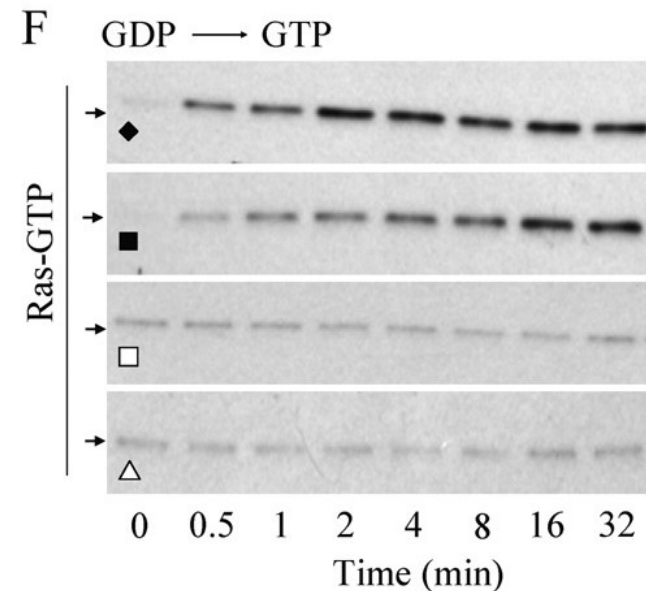
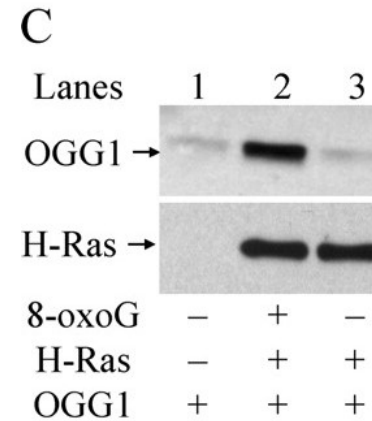
H-Ras protein was loaded with GDP and nucleotide exchange was initiated by adding:

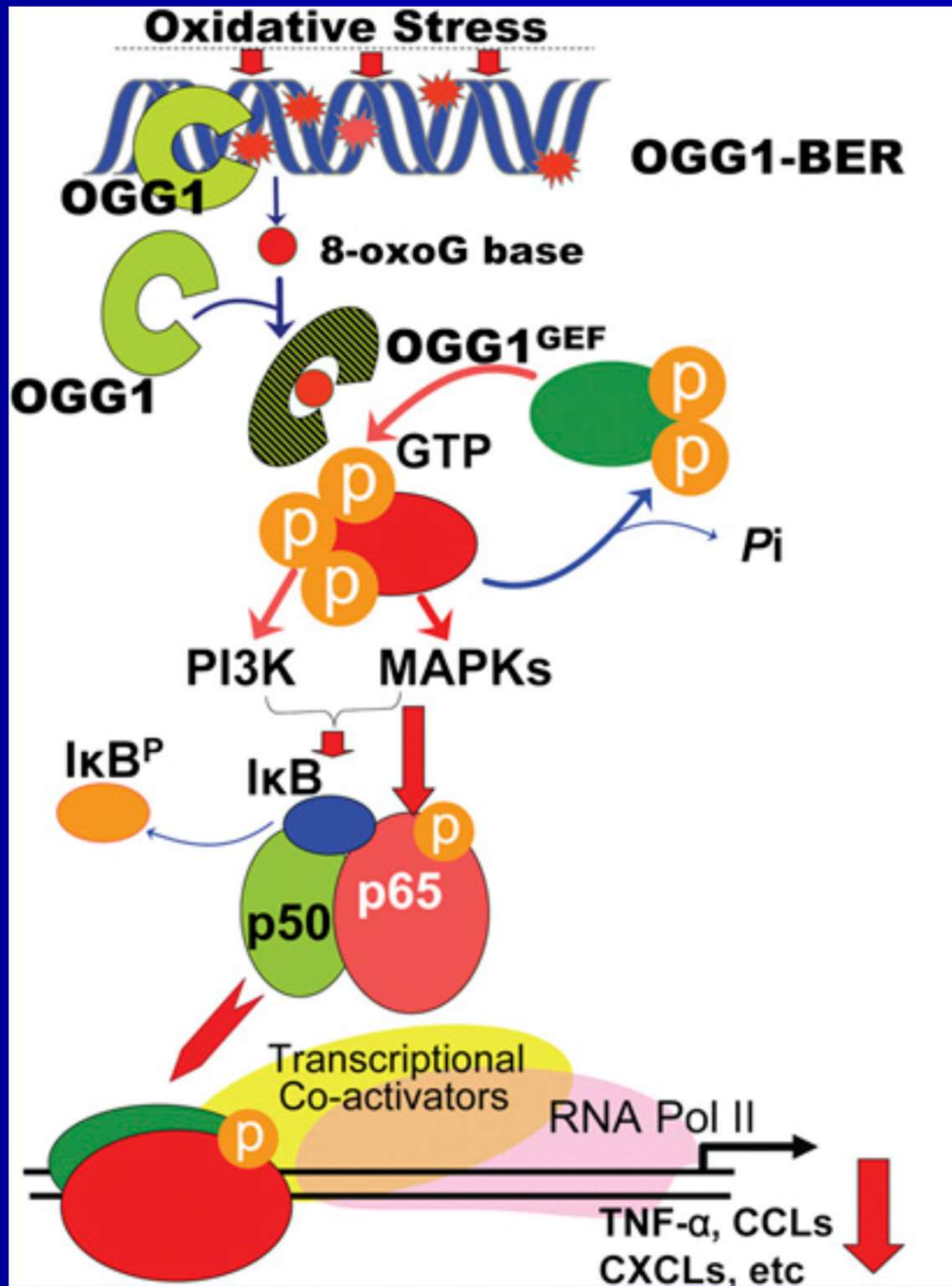
OGG1 (6 pM) plus 8-oxoG (◆)

OGG1 (0.6 pmol) of plus 8-oxoG (■)

OGG1 (□)

8-oxoG (▲)





OGG1 and inflammation

GDP→GTP exchange

RAS-GTP-driven signaling

NF-κB activation

proinflammatory
chemokine/cytokine
expression

OXOGUANINA e TRASCRIZIONE 2

Cells exploit damaged guanine bases and the repair protein to orchestrate a profile of various transcriptomes in redox-regulated biological processes