ヌクレオチド除去修復は酸化的クラスターDNA損傷によって誘発される突然変異を抑制する

佐々　彰，鴨下　渚，兼丸　祐紀，本間　正充，安井　学

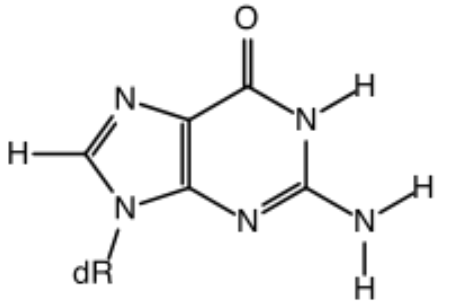
Akira Sassa, Nagisa Kamoshita, Yuki Kanemaru,

Masamitsu Honma, Manabu Yasui

国立医薬品食品衛生研究所　変異遺伝部

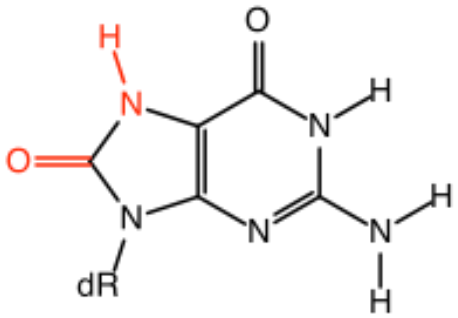
Division of Genetics and Mutagenesis, National Institute of Health Sciences.

Oxidative clustered DNA lesions are induced by ionizing radiation.

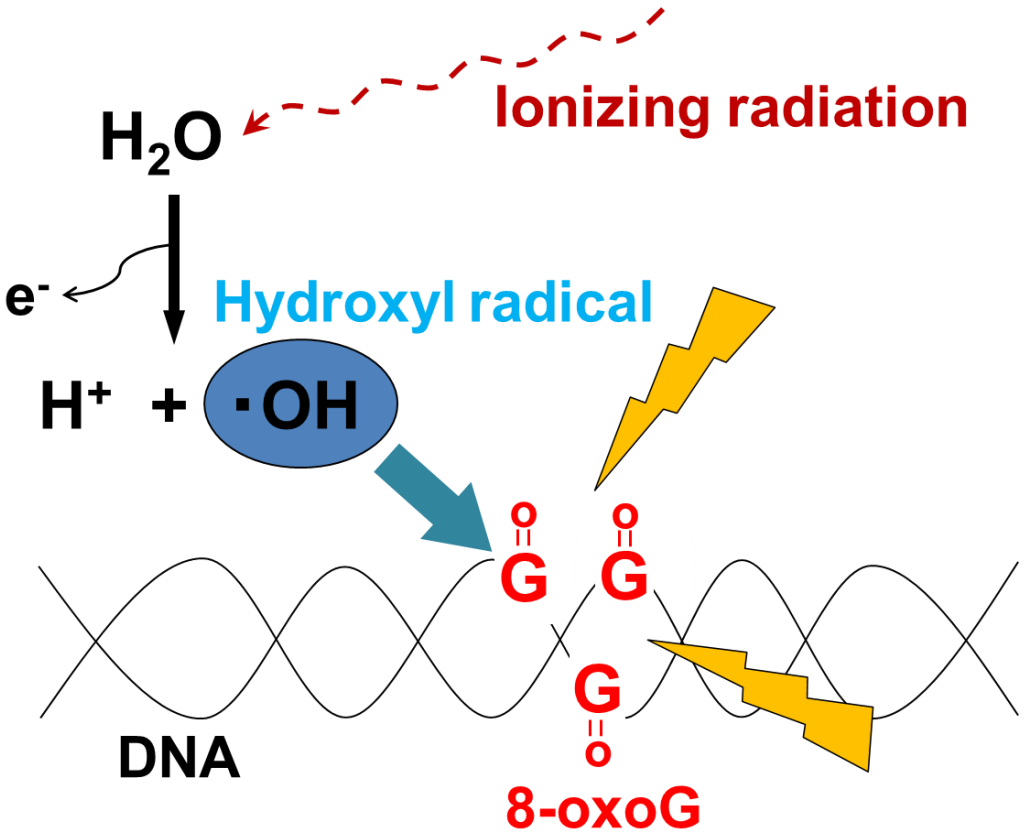


guanine

Oxidative Damage



7,8-dihydro-8-oxoguanine (8-oxoG)

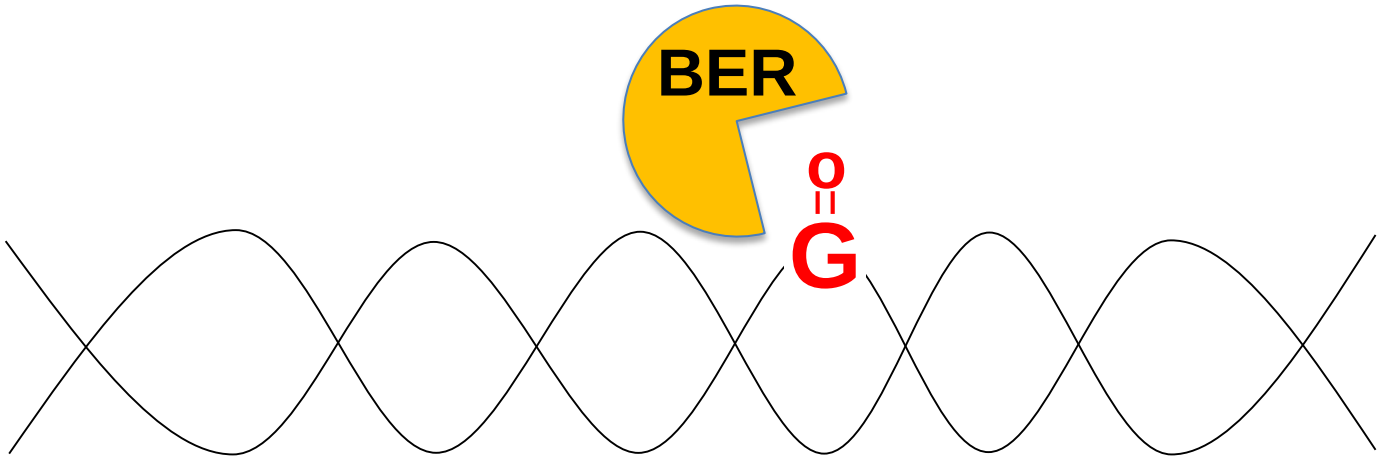


Clustered DNA adducts

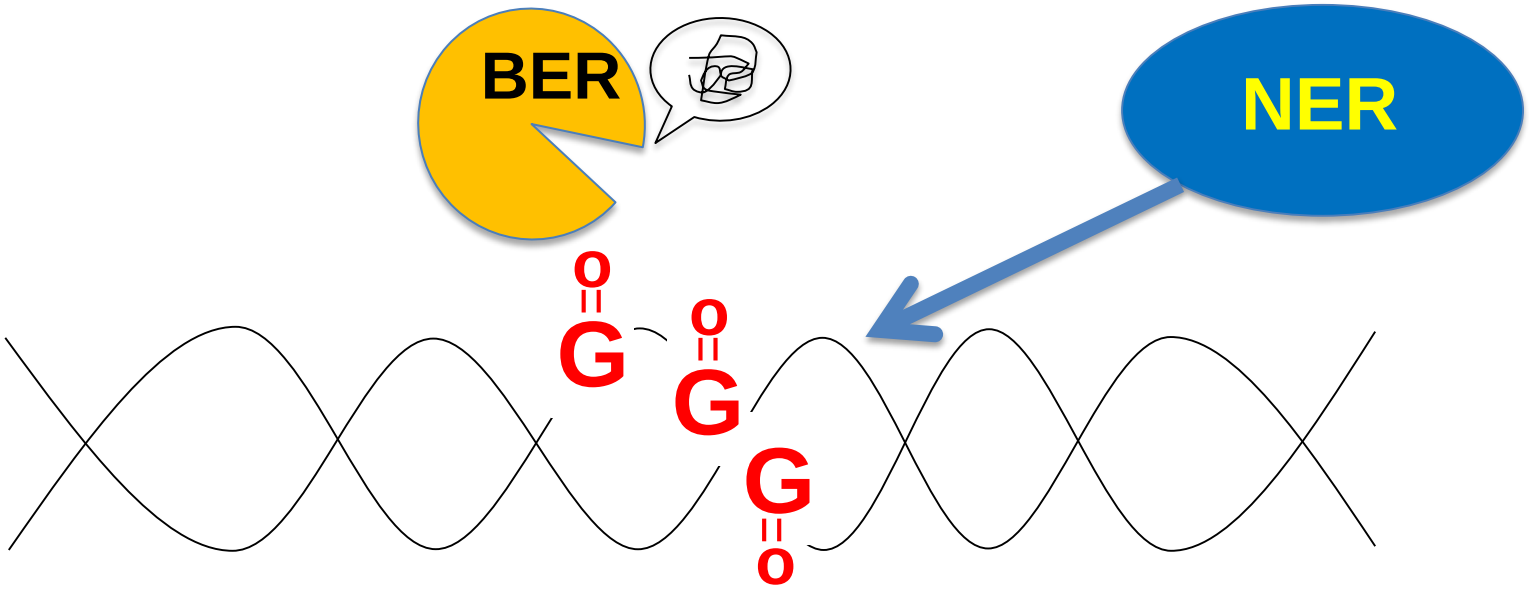
Question

What is the repair mechanisms of oxidative clustered DNA adducts in the human genome?

Model for the repair of clustered 8-oxoG lesions in human cells.

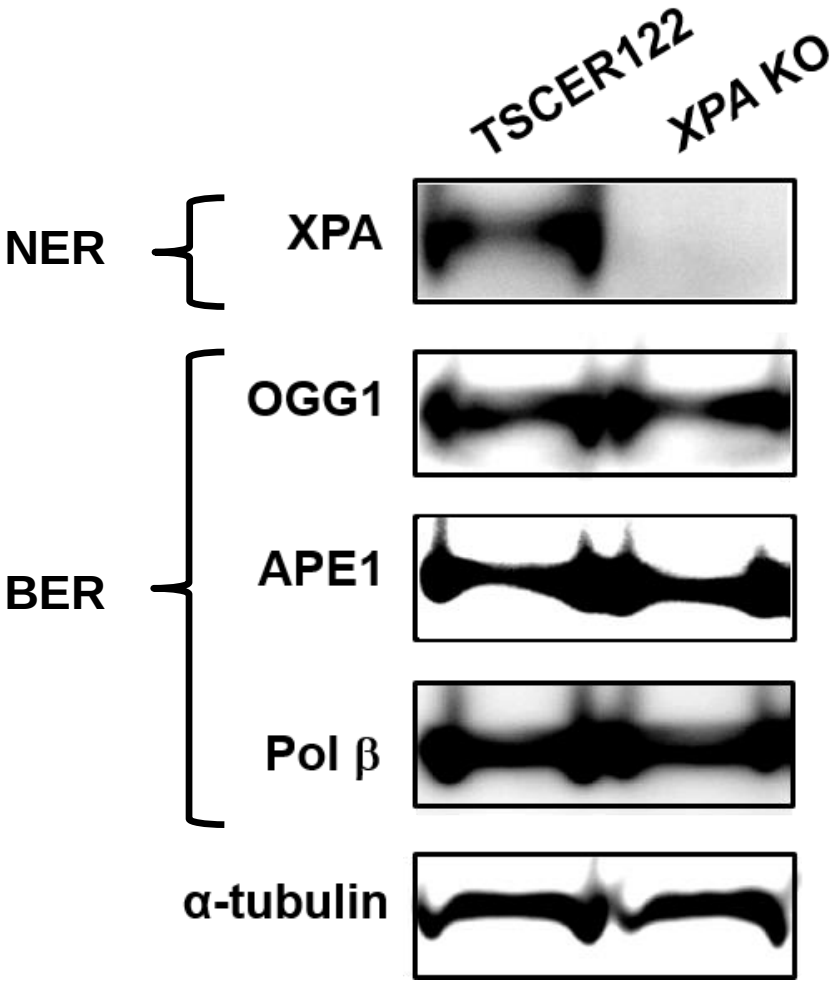


A single 8-oxoG is primarily repaired by base excision repair (BER).



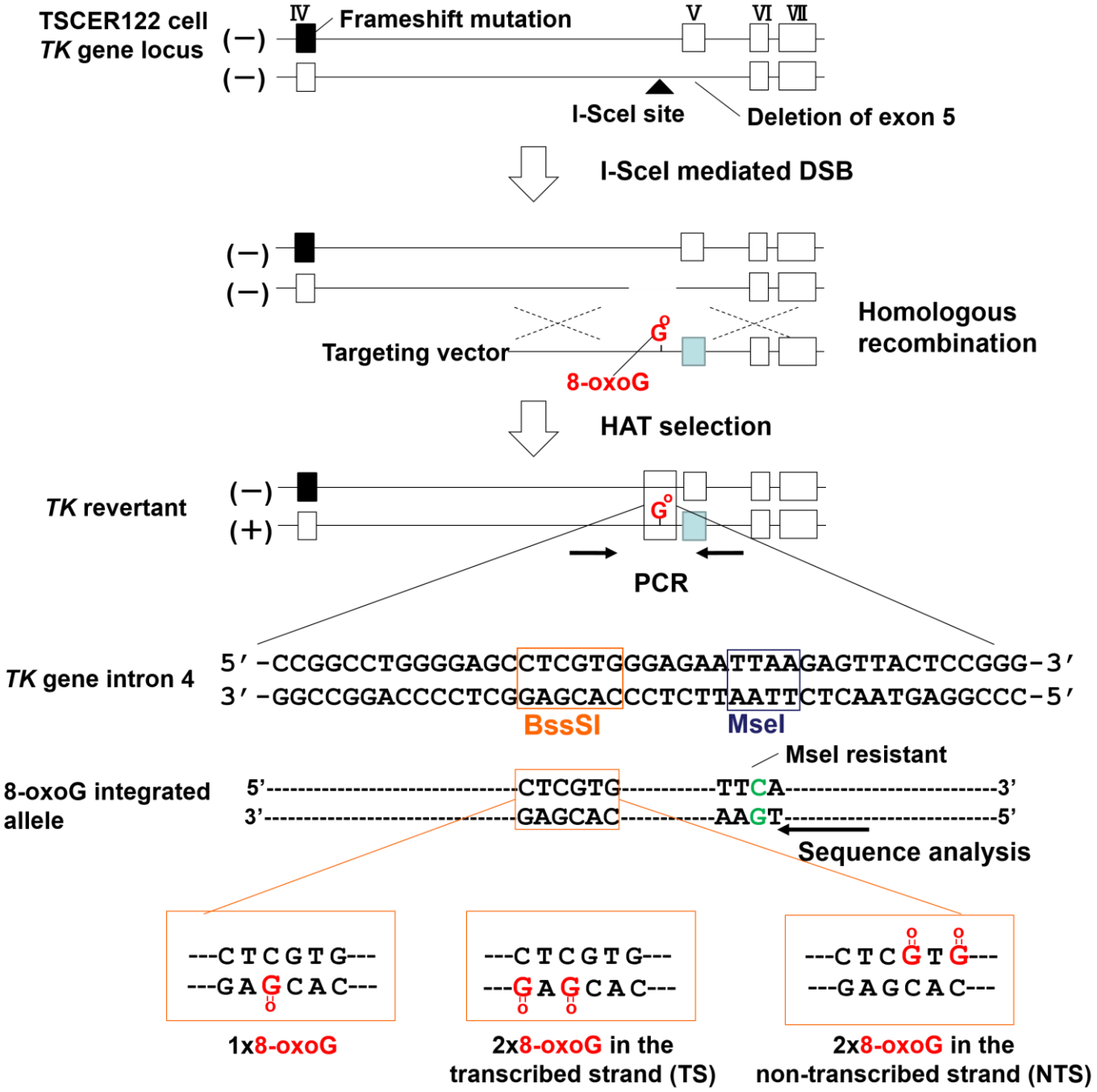
Can clustered 8-oxoG be repaired by the different mechanism such as nucleotide excision repair (NER)?

Disruption of xeroderma pigmentosum group A (*XPA*), essential gene for NER, in human lymphoblastoid TSCER122 cells

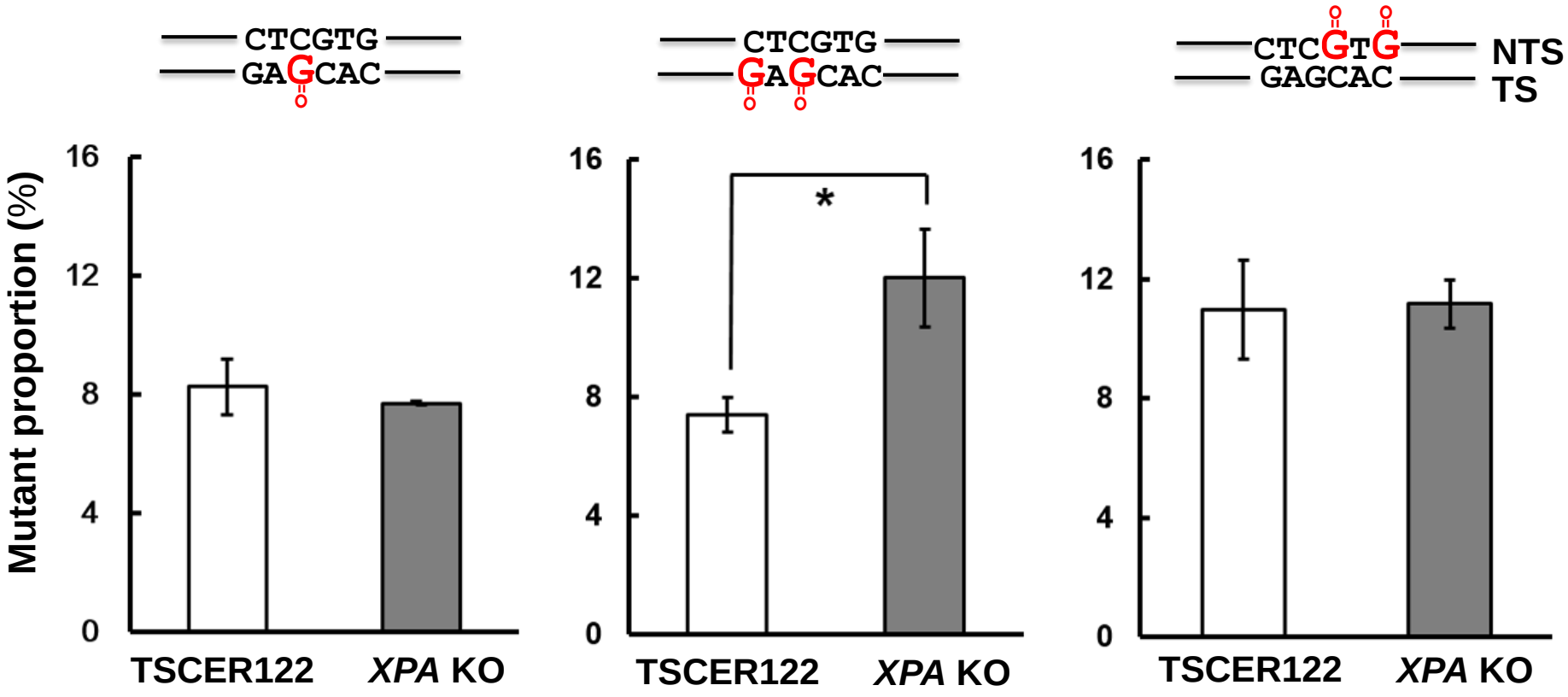


- XPA was expressed in TSCER122 cells but not in *XPA* KO cells.
- Expression of BER proteins was not altered by the disruption of *XPA*.

Tracing DNA Adducts in TArgeted Mutagenesis (TATAM) system.

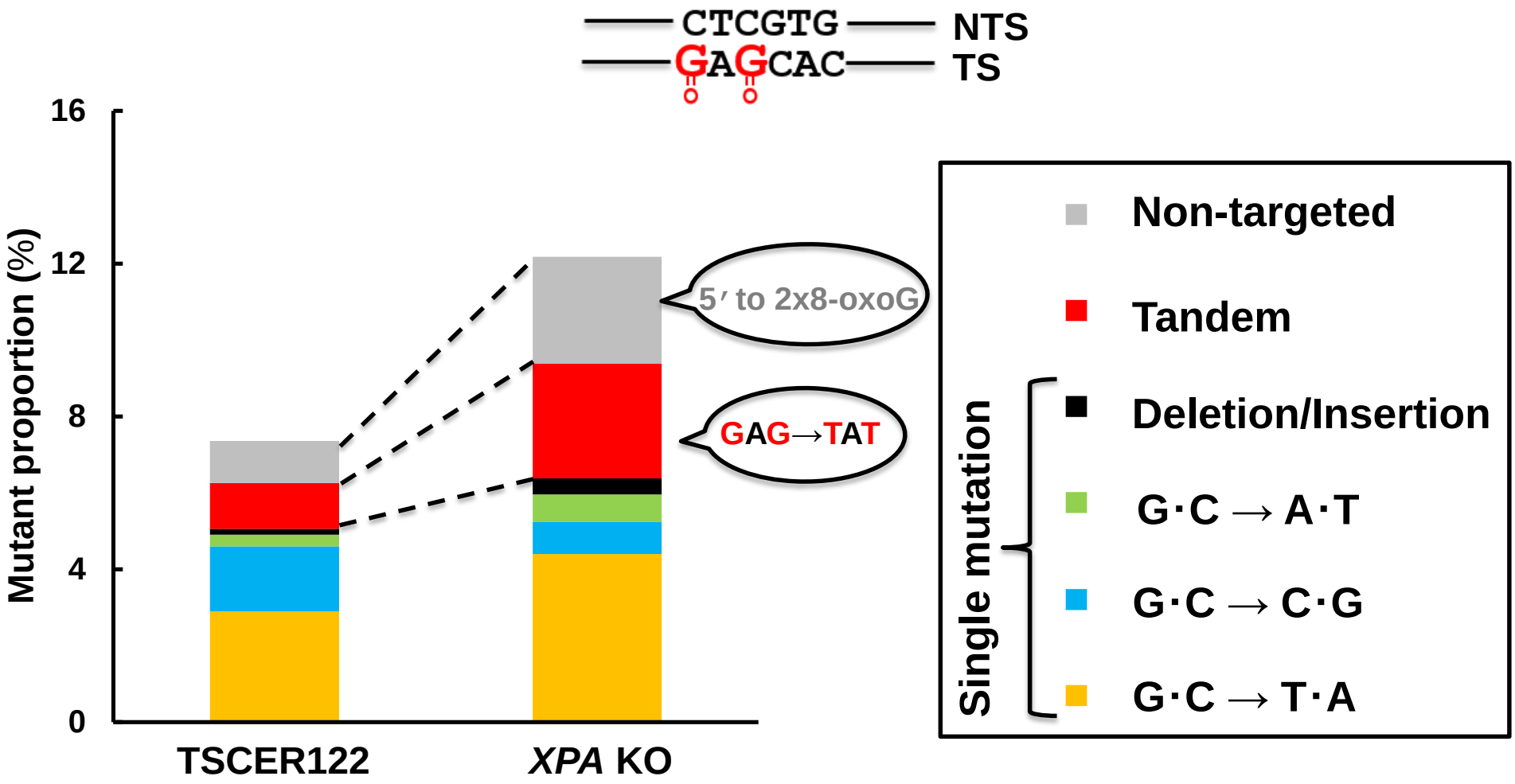


Mutant proportions induced by integration of 1x8-oxoG, 2x8-oxoG in TS, and 2x8-oxoG in NTS.



The lack of *XPA* significantly enhanced the mutant proportion of 2x8-oxoG in TS compared with that in TSCER122 cells, but not in TNS.

Mutation spectra induced by 2x8-oxoG in TS.



The proportions of Tandem and Non-targeted mutations were markedly increased in *XPA* KO cells.

Summary & Discussion

1. **The mutant proportion induced by a single 8-oxoG was comparable between TSCER122 and *XPA* KO cells.**

2. **The knock-out of *XPA* significantly increased the mutant proportion of 2x8-oxoG in the transcribed strand. Especially, the proportions of tandem and non-targeted mutations were markedly increased.**

3. ***XPA* disruption did not influence the mutant proportion of 2x8-oxoG in the non-transcribed strand.**

↓

Transcription-coupled nucleotide excision repair is involved in the repair of clustered DNA adducts in the genome.

(Sassa et al., *PLoS ONE* (2015), e0142218)