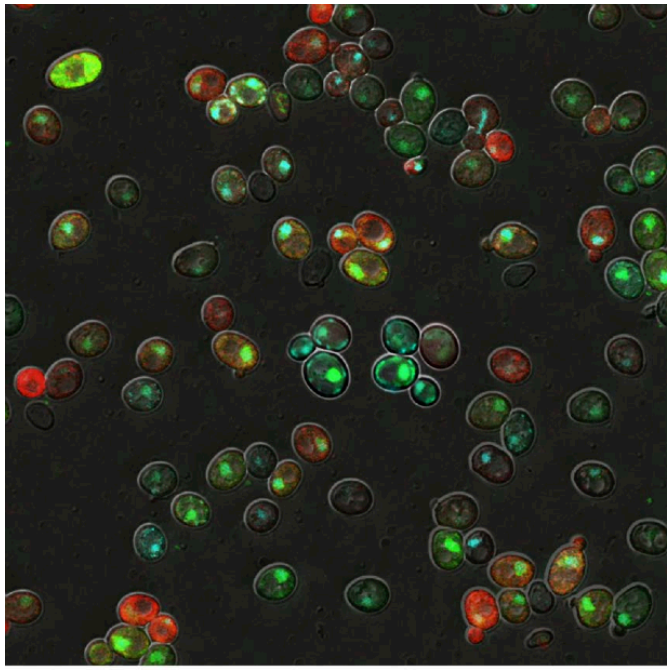
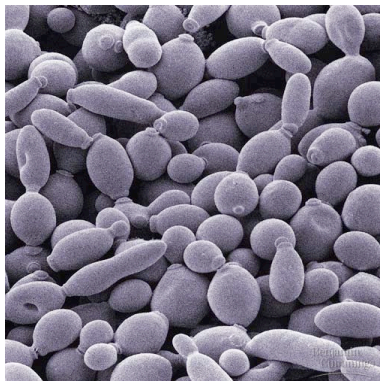
Regulation of Eukaryotic Base Excision Repair via Dynamic Compartmentalization



Paul W. Doetsch

Emory University School of Medicine

Saccharomyces cerevisiae: a useful model organism for understanding the biological consequences of DNA damage



1. DNA damage causes an increase in intracellular ROS
(signaling and / or oxidative stress)

2. Yap1 is a DNA damage responder
(via ROS signaling)

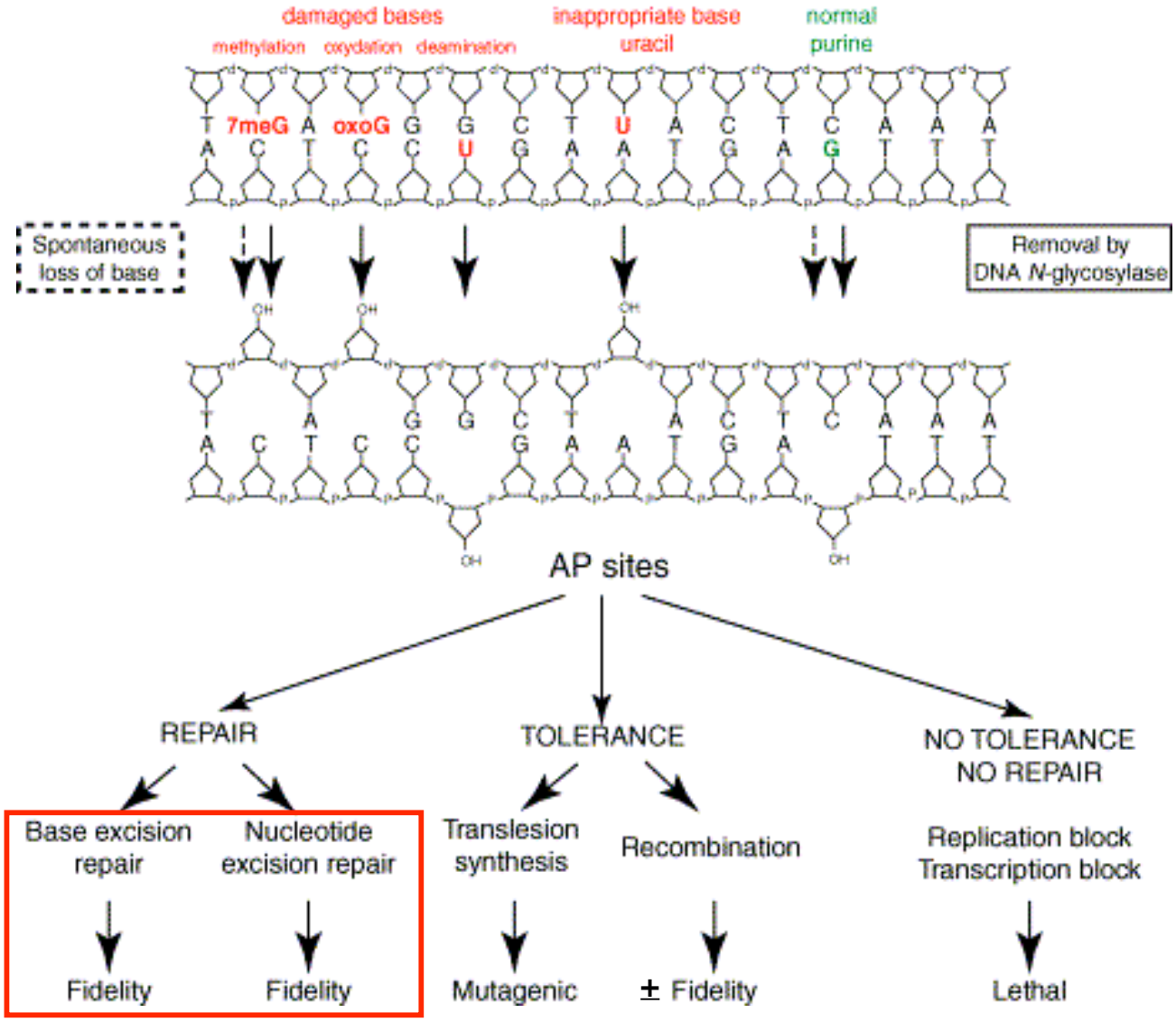
3. Nuclear and mitochondrial oxidative DNA damage regulate BER
(dynamic compartmentalization; participants include Ntg1, importin alpha, beta)

4. Chronic DNA damage causes profound chromosomal instability
(via oxidative stress)

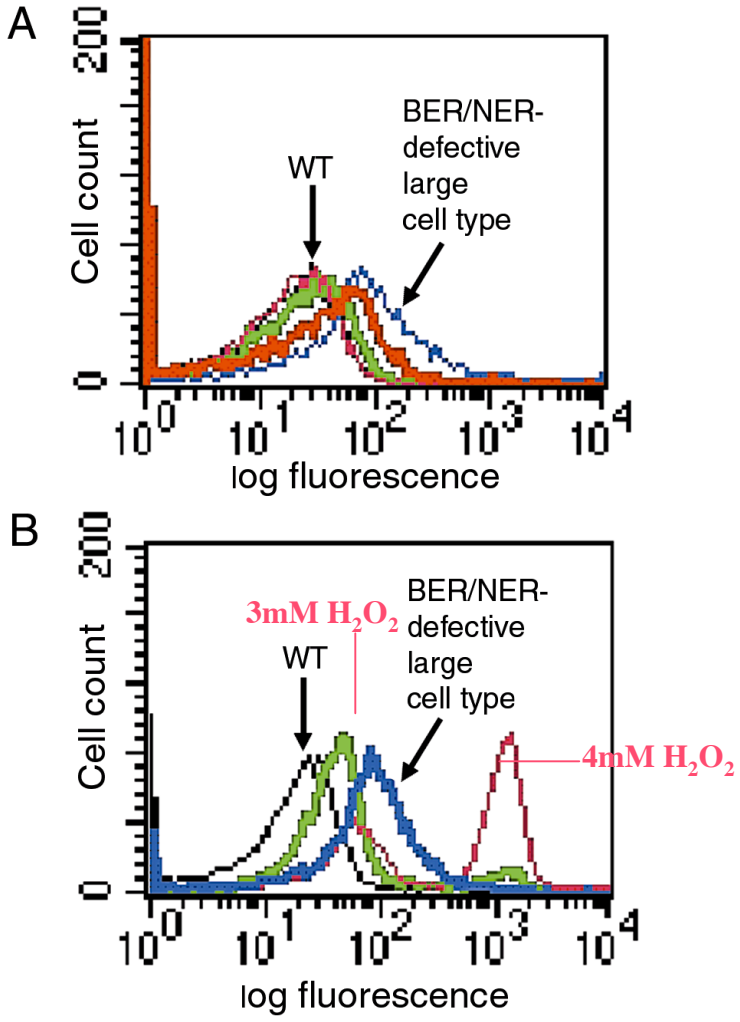
Publications directly related to this talk

- Evert et al., *J. Biol. Chem.* 279: 22585-22594 (2004)
- Salmon et al., *Nucleic Acids Res.* 32: 3712-3723 (2004)
- Rowe et al., *Free Radical Biol. Med.* 45: 1167-1177 (2008)
- Degtyareva et al., *Mol. Cell. Biol.* 28: 5432-5445 (2008)
- Griffiths et al., *Mol. Cell. Biol.* 29: 794-807 (2009)

DNA Repair Pathways



Elevated intracellular ROS levels in BER/NER-defective cells

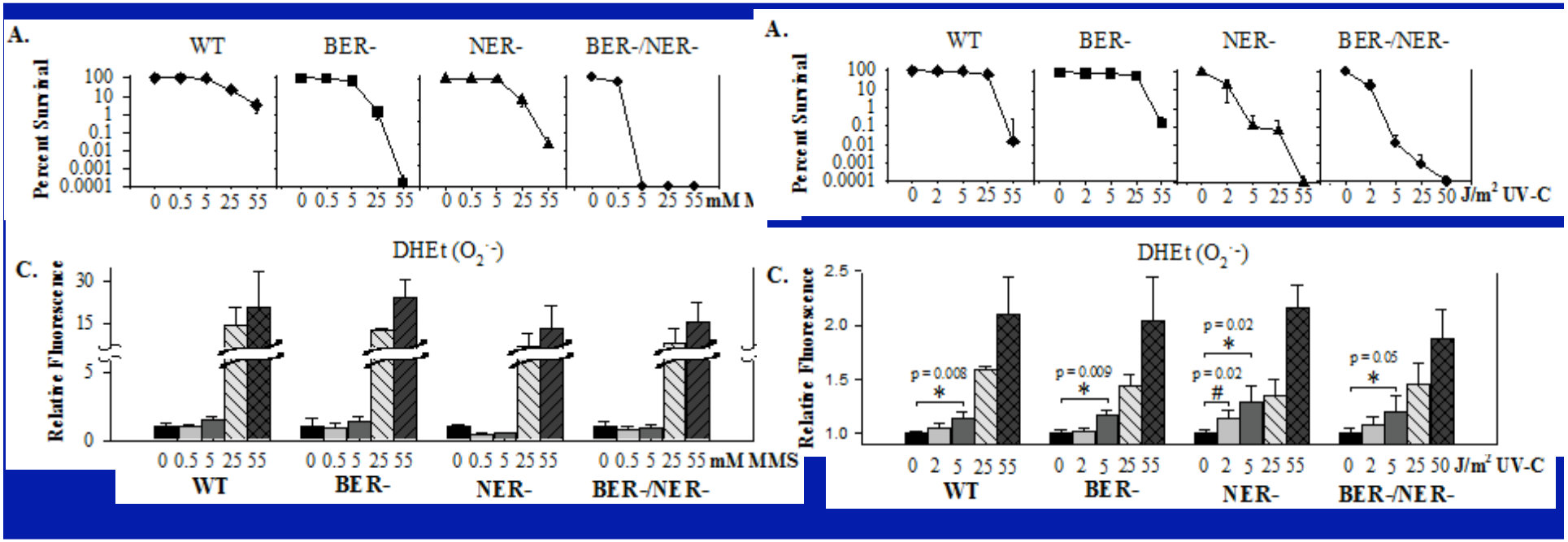


BER- / NER-defective cells harbor high levels of oxidative DNA damage

TABLE I
Ntg1p-recognized DNA lesions in the CAN1 locus and the overall genome

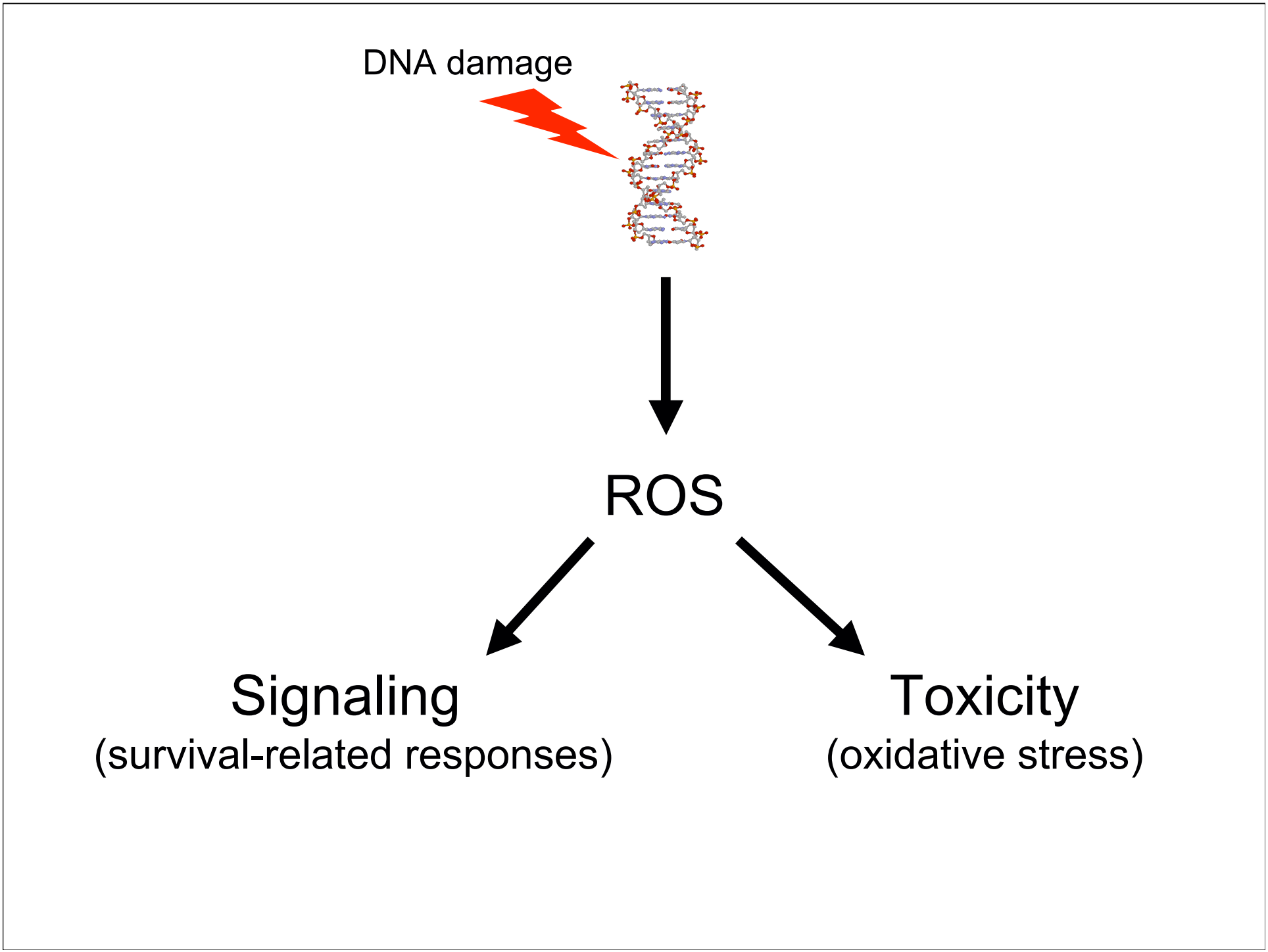
Strain	Ratio of band intensities of Ntg1p treated to untreated samples[a]		Lesions per 3.7kb *CAN1* fragment[b]		Lesions per genome[c]	
	24 h[d]	72 h[d]	24 h	72 h	24 h	72 h
WT	1.0 ± 0.030	0.84 ± 0.043	0	0.17	0	550
BER-defective	0.89 ± 0.061	0.70 ± 0.054	0.12	0.36	380	1170
NER-defective	1.0 ± 0.060	0.78 ± 0.028	0	0.25	0	810
BER/NER-defective mixed cell type	0.77 ± 0.039	ND[e]	0.26	ND	840	ND
BER/NER-defective large cell type	0.65 ± 0.044	0.56 ± 0.032	0.43	0.58	1400	1880
WT H_2O_2	0.66 ± 0.051	ND	0.42	ND	1360	ND

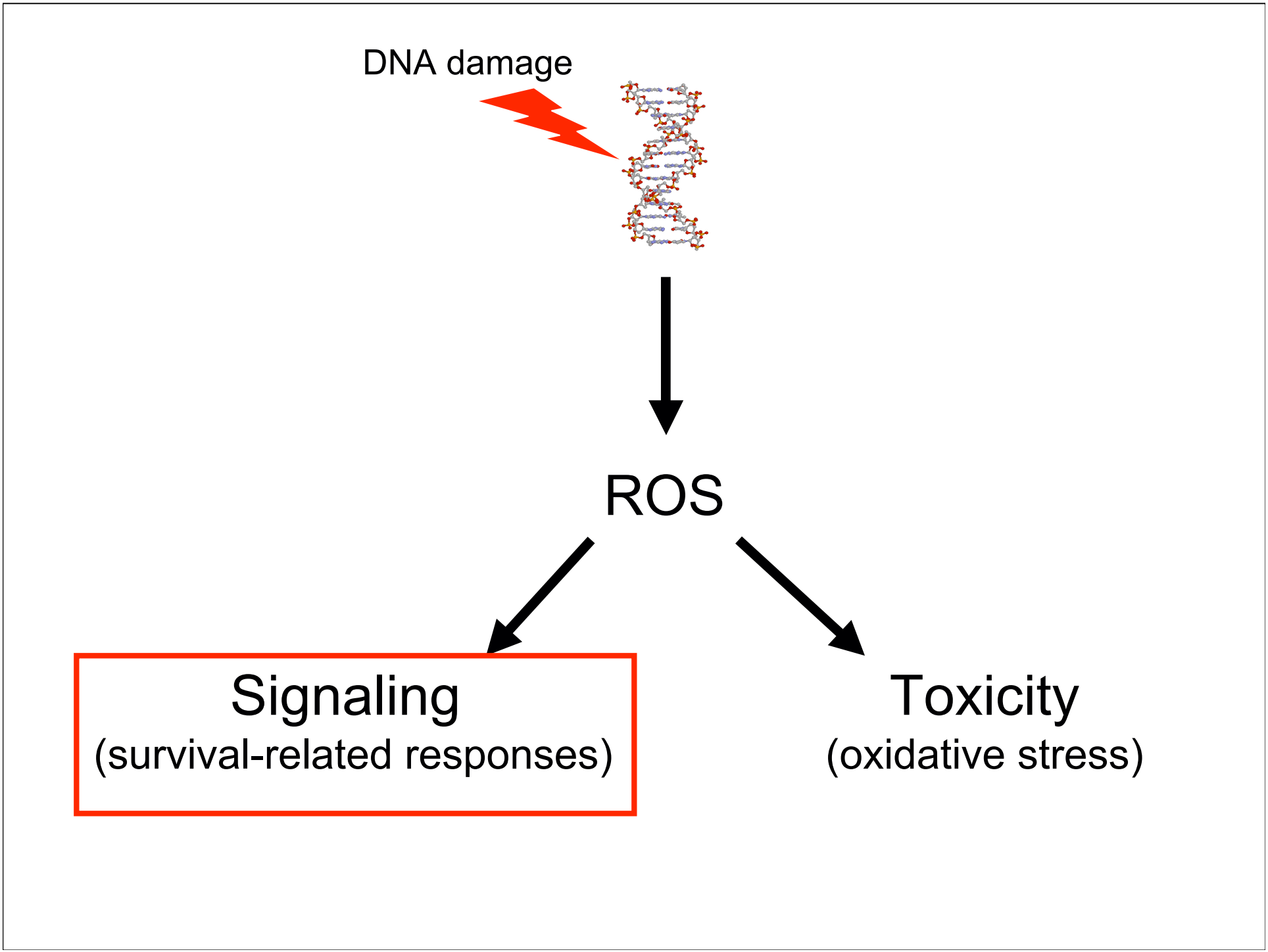
Intracellular ROS levels in repair deficient strains following exposure to MMS and UV-C



- Intracellular $O_2^{\bullet -}$ levels increase in all strains regardless of repair background in response to both MMS and UV-C

-The increase in intracellular ROS is independent of cell death


DNA damage
ROS
Signaling
(survival-related responses)
Toxicity
(oxidative stress)


DNA damage
ROS
Signaling
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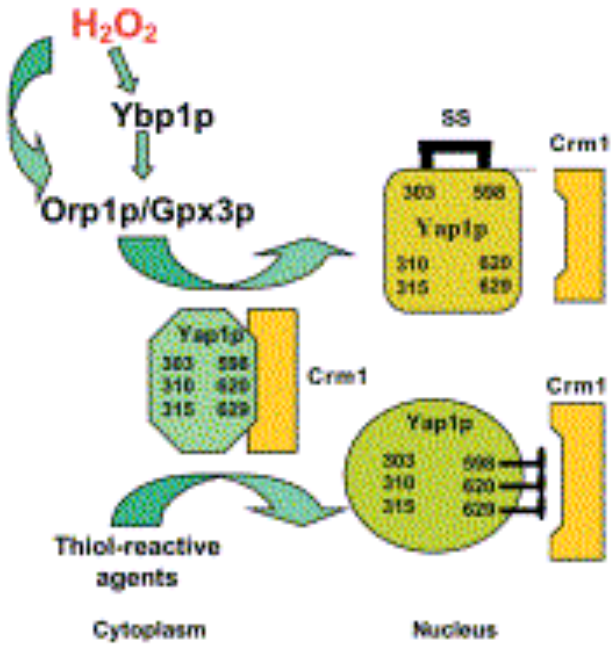
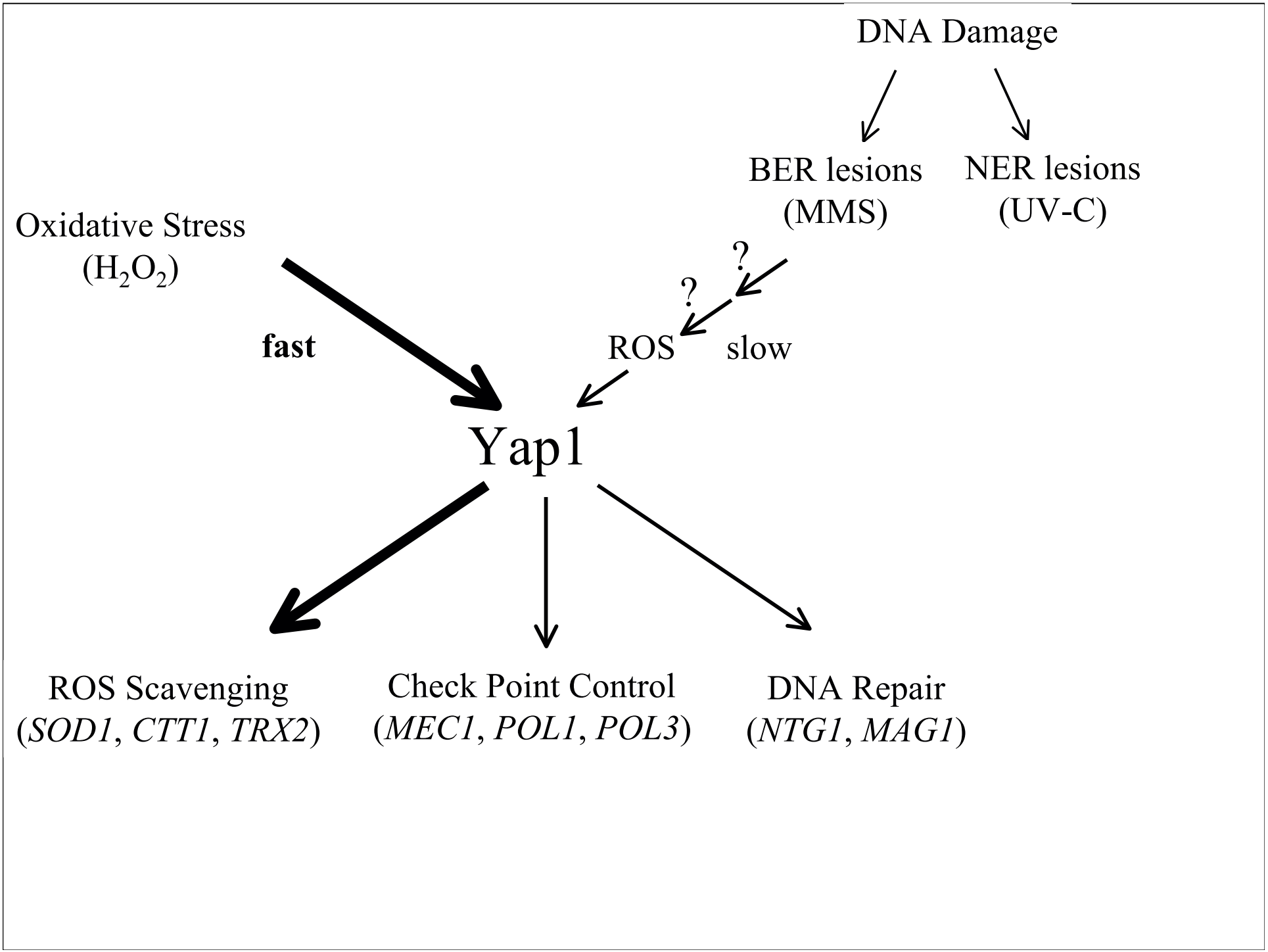
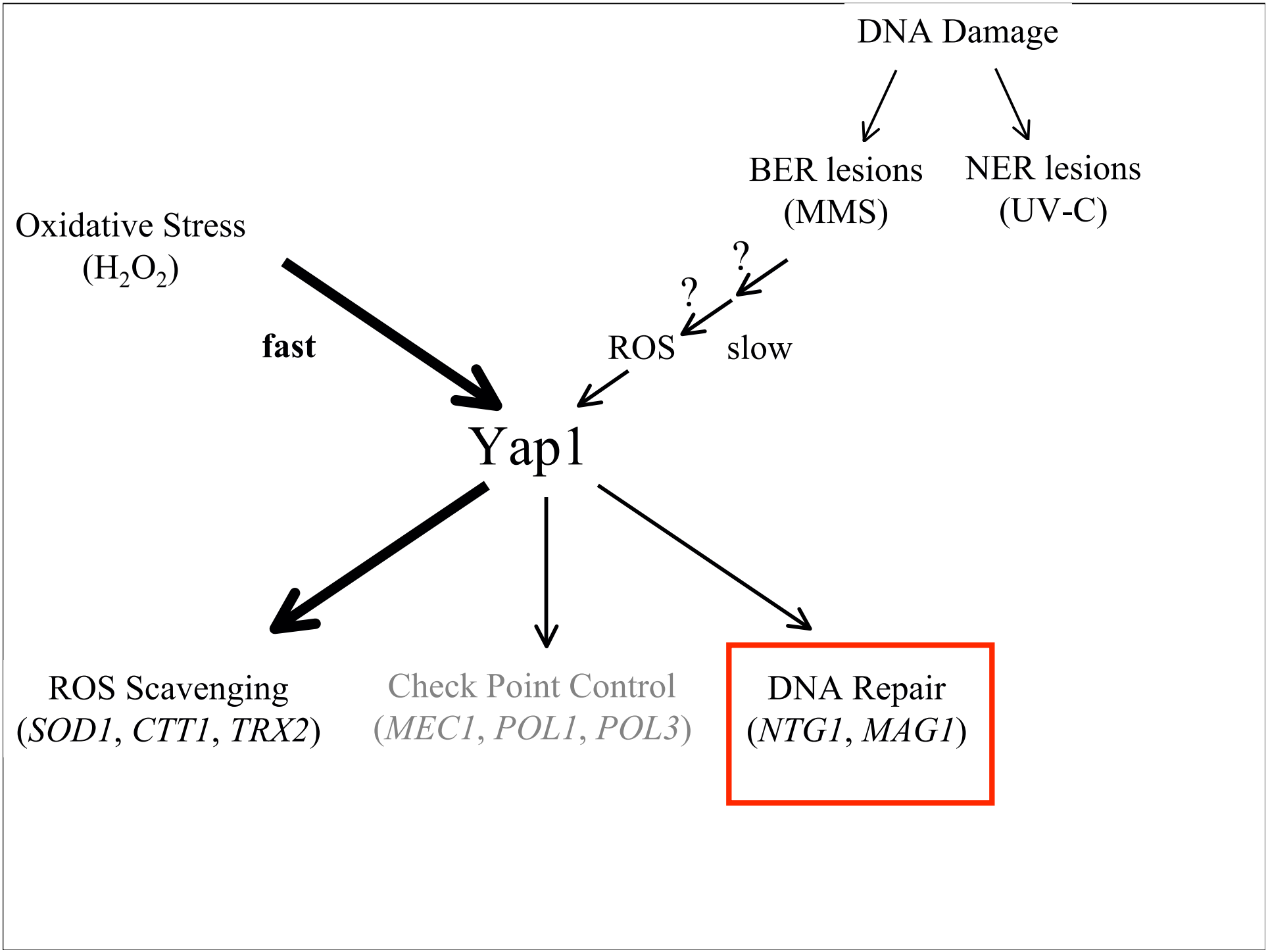
Toxicity
(oxidative stress)

Yap1



- Transcription factor that senses levels of H_2O_2 present in yeast cells
- In response to H_2O_2 Yap1 activates transcription of genes that mitigate oxidative stress
- Mainly localized to cytoplasm under non-stress conditions through its continuous export from nucleus by Crm1
- In response to H_2O_2 intramolecular disulfide bonds form in Yap1 and Crm1 no longer binds allowing for nuclear accumulation


DNA Damage
BER lesions
(MMS)
NER lesions
(UV-C)
Oxidative Stress
(H_2O_2)
?
?
fast
ROS
slow
Yap1
ROS Scavenging
(*SOD1*, *CTT1*, *TRX2*)
Check Point Control
(*MEC1*, *POL1*, *POL3*)
DNA Repair
(*NTG1*, *MAG1*)


DNA Damage
BER lesions
(MMS)
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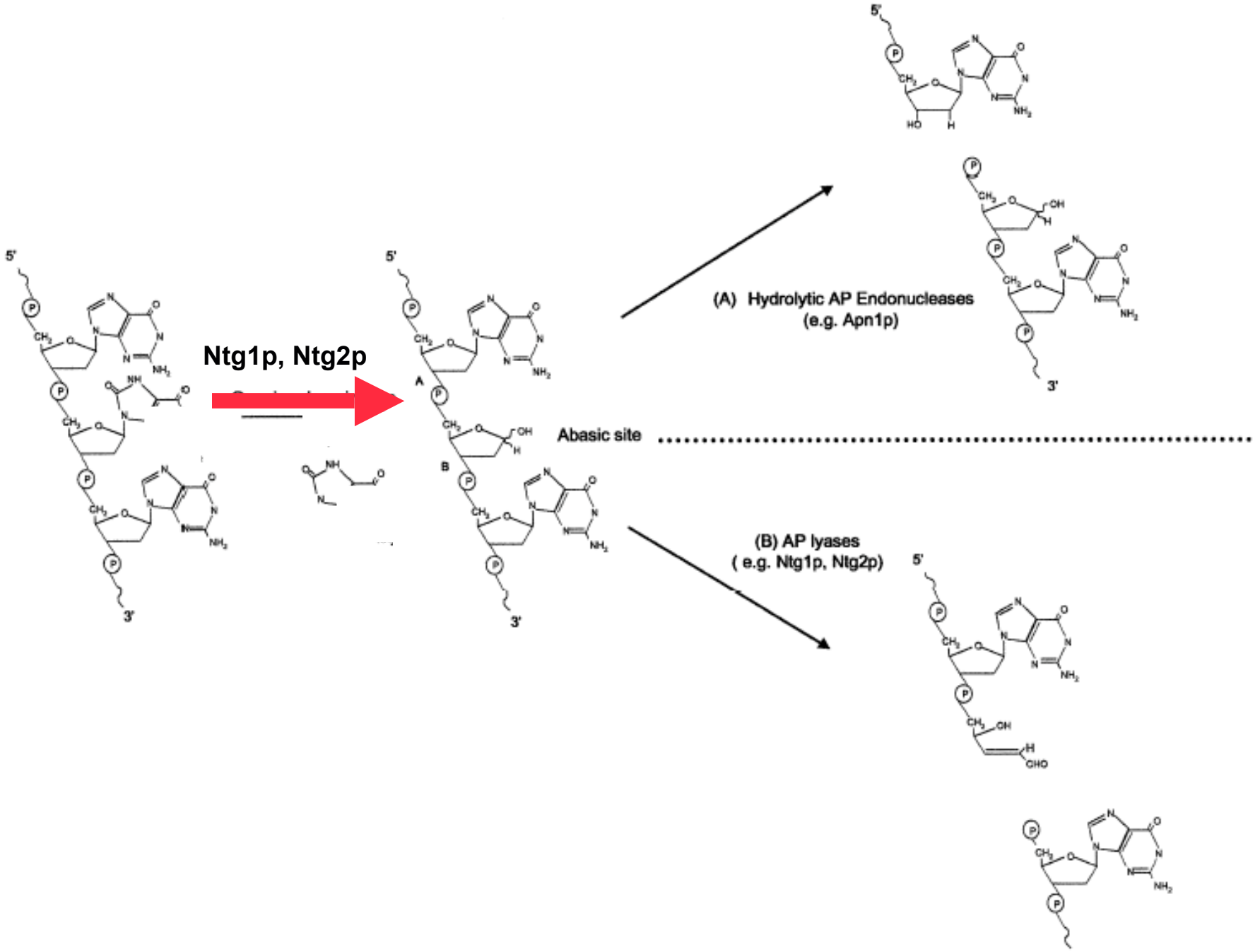
Ntg1p, Ntg2p
Abasic site
(A) Hydrolytic AP Endonucleases
(e.g. Apn1p)
(B) AP lyases
(e.g. Ntg1p, Ntg2p)
5'
3'
A
B

Amino Acid Sequence of Ntg1 and Ntg2

Putative NLS
Putative MTS
Catalytic domain
Putative active site lysine
Iron-sulfur center
Putative sumoylation sites

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Ntg1
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101 ARMRVLRSKI LAPVDIIGGS SIPVTVASKC GISKEQISPR DYRLQVLLGV 150
151 MLSSQTKDEV TAMAMLNIMR YCIDELHSEE GMTLEAVLQI NETKLDELIH 200
201 SVGFHTRKAK YILSTCKILQ DQFSSDVPAT INELLGLPGV GPKMAYLTLQ 250
251 KAWGKIEGIC VDVHVDRLTK LWKWVDAQKC KTPDQTRTQL QNWLPKGLWT 300
301 EINGLLVGFG QIITKSRNLG DMLQFLPPDD PRSSLDWDLQ SQLYKEIQQN 350
351 IMSYPKWVKY LEGKRELNVE AEINVKHEEK TVEETMVKLE NDISVKVED

Ntg2
  1 MREESRSRKR KHIPVDIEEV EVRSKYFKKN ERTVELVKEN KINKDLQNYG  50
 51 GVNIDWIKAL KPIEYFEWIE SRTCDDPRTW GRPITKEEMI NDSGAKVPES 100
101 FLPIYNRVRL MRSKVKTPVD AMGCSMIPVL VSNKCGIPSE KVDPKNFRLQ 150
151 FLIGTMLSAQ TRDERMAQAA LNITEYCLNT LKIAEGITLD GLLKIDEPVL 200
201 ANLIRCVSFY TRKANFIKRT AQLLVDNFDS DIPYDIEGIL SLPGVGPKMG 250
251 YLTLQKGWGL IAGICVDVHV HRLCKMWNWV DPIKCKTAEH TRKELQVWLP 300
301 HSLWYEINTV LVGFGQLICM ARGKRCDLCL ANDVCNARNE KLIESSKFHQ 350
351 LEDKEDIEKV YSHWLDTVTN GITTERHKKK
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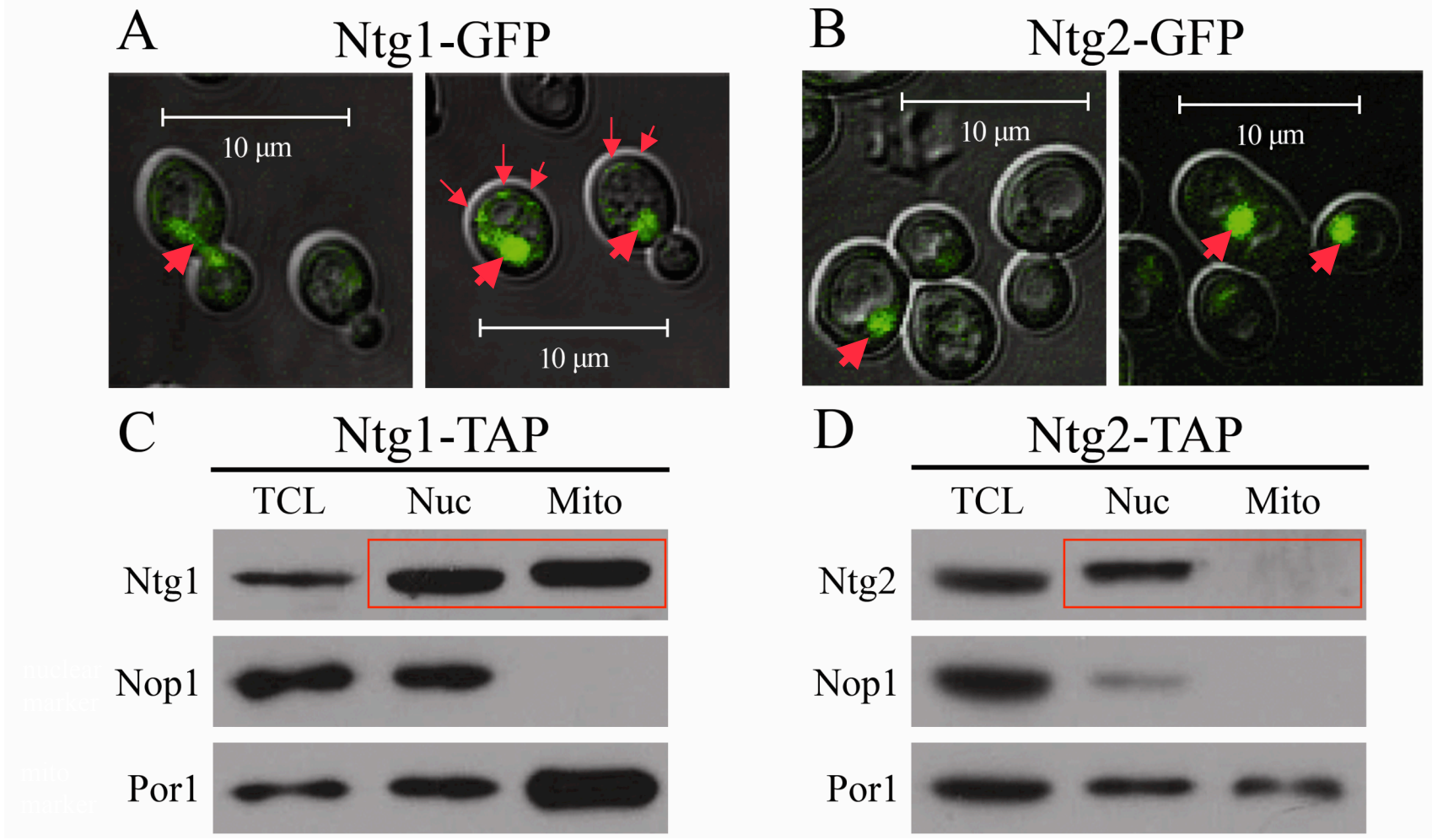
Localization of Ntg1 and Ntg2



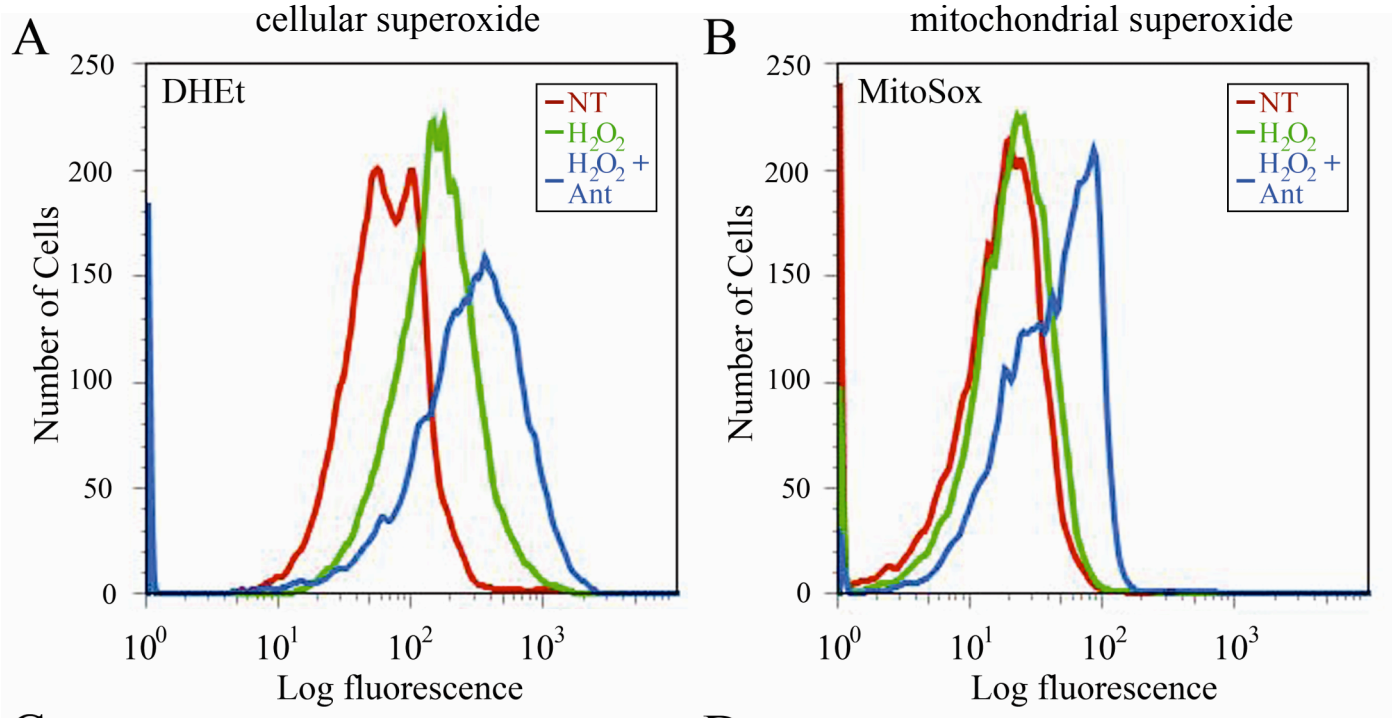
Regulation of BER Proteins

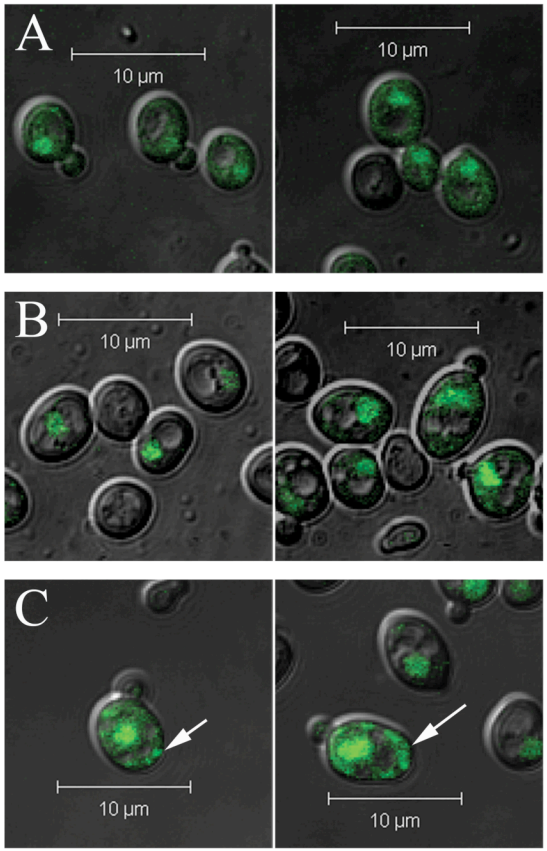
1. Is the localization of BER proteins affected by levels of oxidative DNA damage in the nucleus or mitochondria?
2. Is post-translational modification a mechanism of regulation for BER proteins?

H_2O_2 and antimycin can be used to modify nuclear and mitochondrial ROS levels

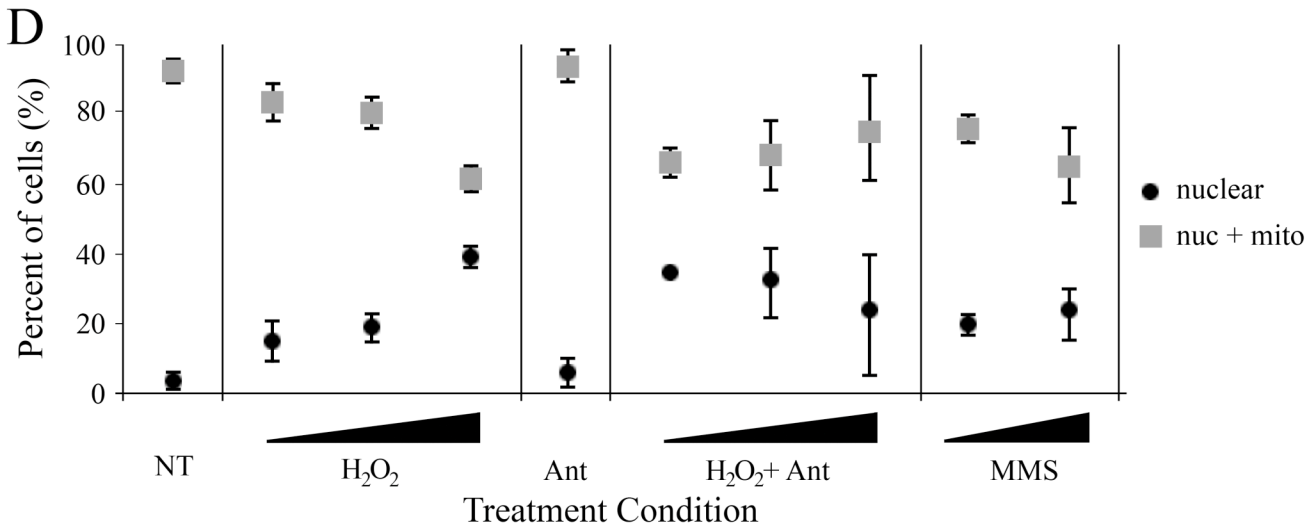
H_2O_2 increases nuclear, but not mitochondrial superoxide levels.

H_2O_2 + Ant increases cellular superoxide levels, including mitochondrial levels.

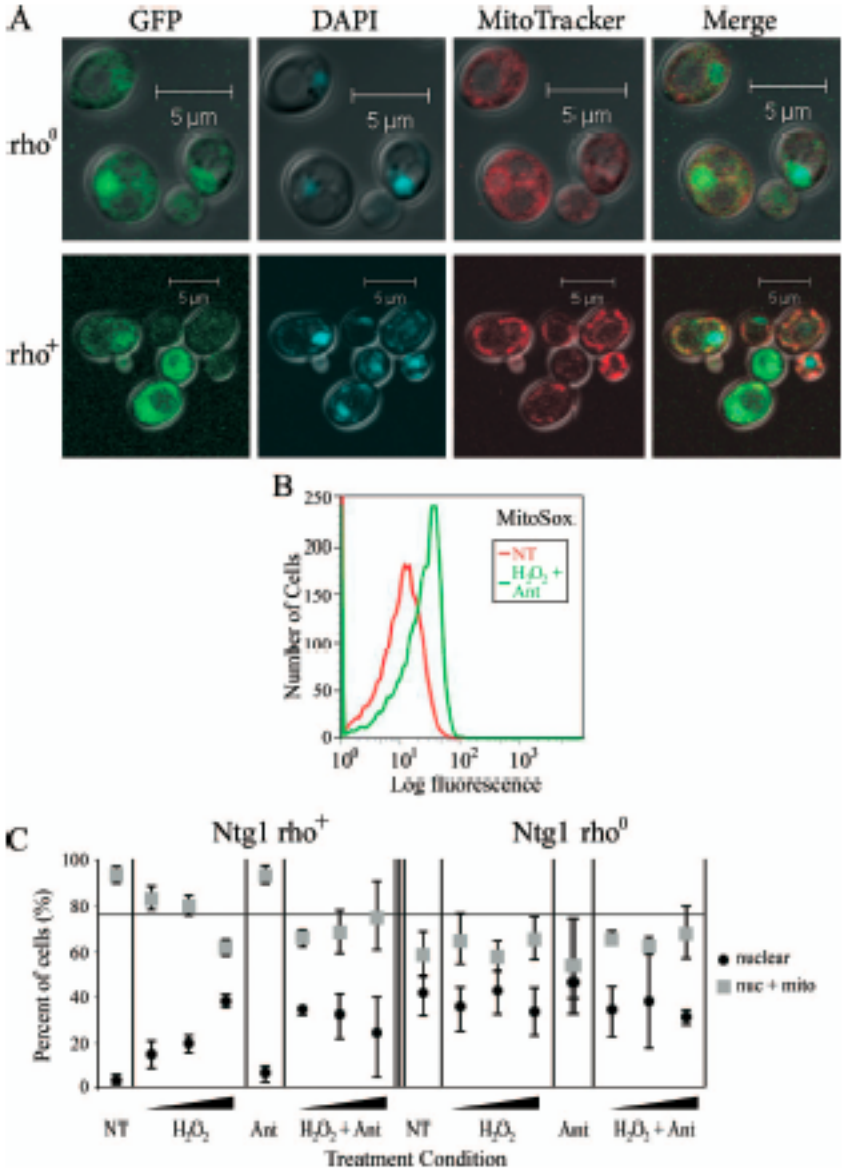




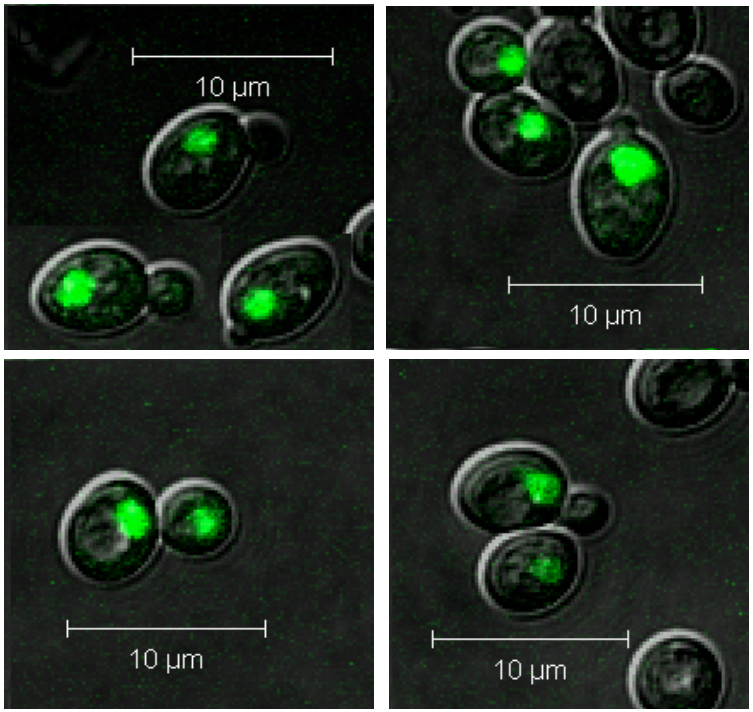
Dynamic relocalization of Ntg1 occurs in response to nuclear and mitochondrial oxidative stress



Mitochondrial localization of Ntg1 is influenced by mitochondrial oxidative DNA damage



No change in Ntg2 localization occurs with introduction of exogenous ROS



Amino Acid Sequence of Ntg1 and Ntg2

Putative NLS
Putative MTS
Catalytic domain
Putative active site lysine
Iron-sulfur center
Putative sumoylation sites

```
Ntg1
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351 LEDKEDIEKV YSHWLDTVTN GITTERHKKK
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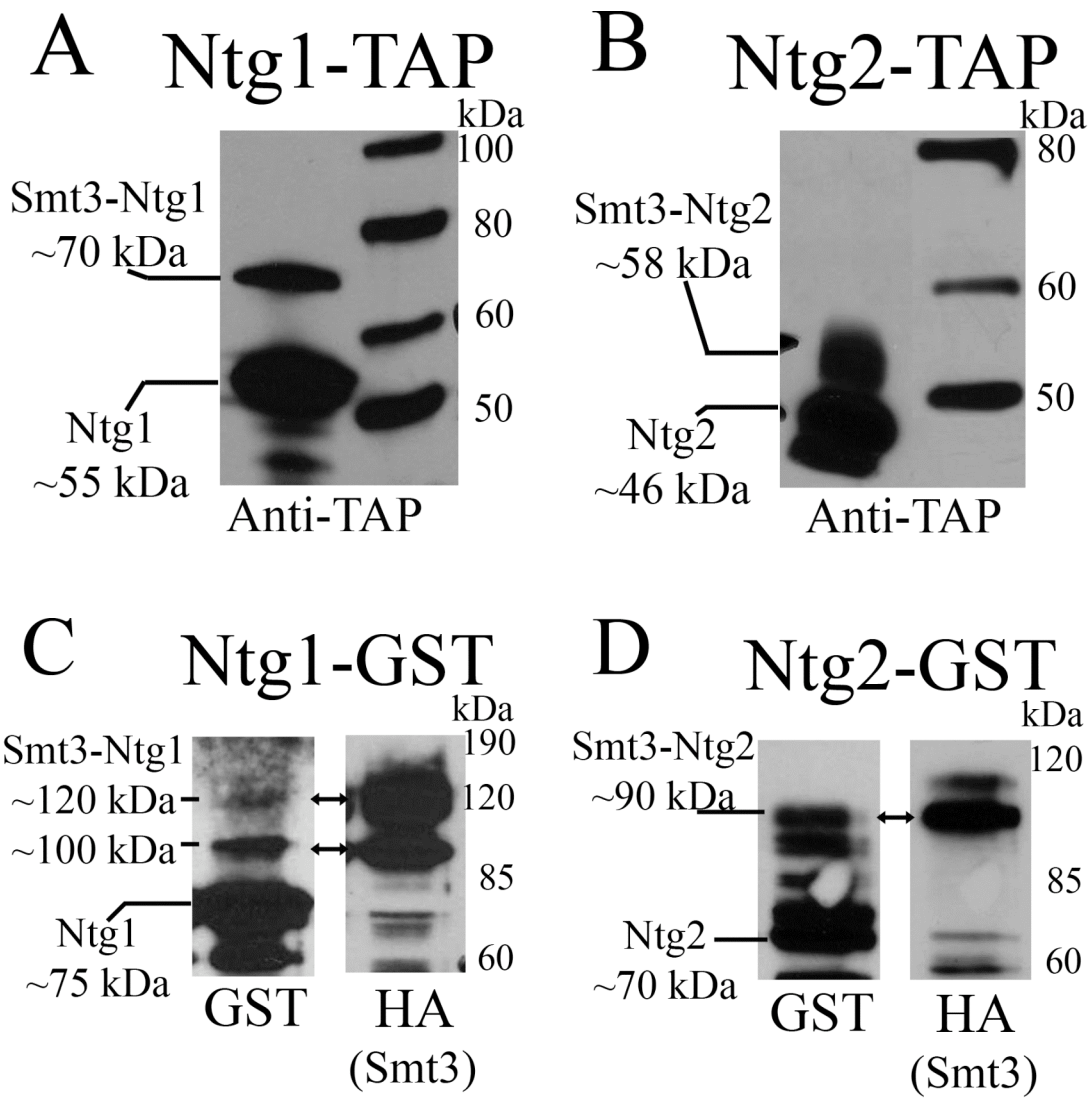
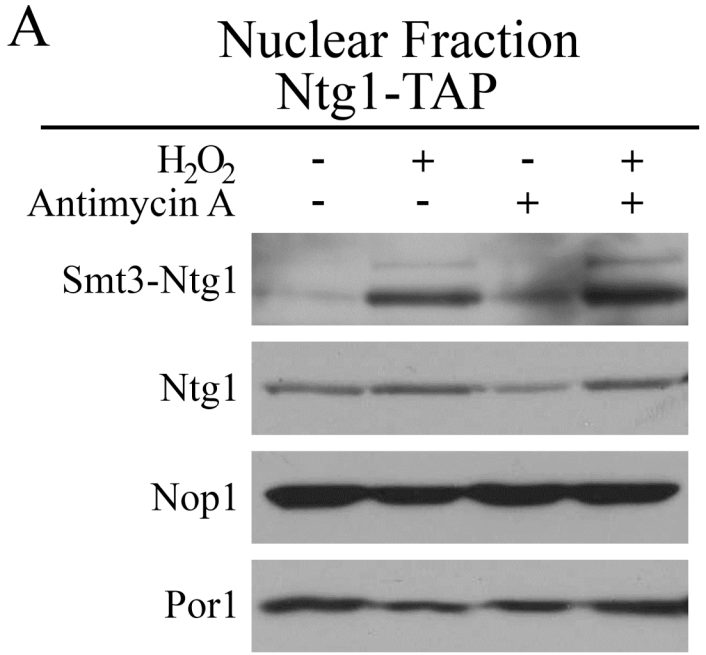
1. **Are Ntg1 and Ntg2 sumoylated?**

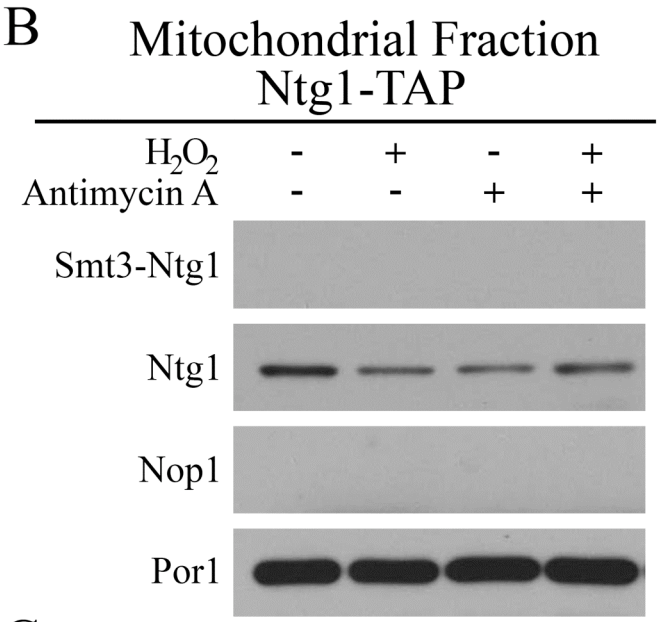
2. **Does sumoylation affect dynamic localization?**

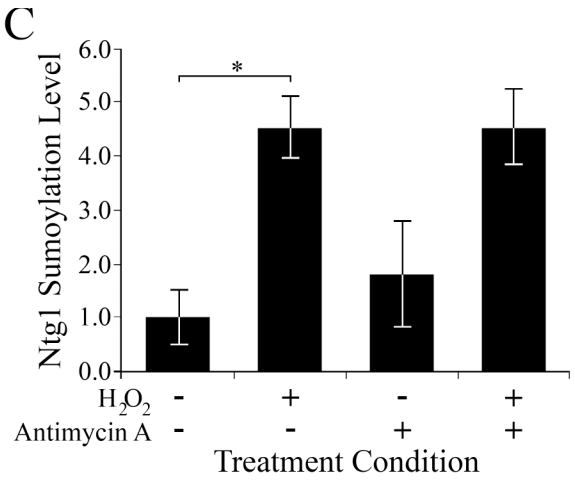
Evidence Supporting Sumoylation of Ntg1 and Ntg2



A higher molecular weight form of Ntg1 is induced by oxidative stress and is nuclear







Dan Swartzlander

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301 HSLWYEINTV LVGFGQLICM ARGKRCDLCL ANDVCNARNE KLIESSKFHQ 350
351 LEDKEDIEKV YSHWLDTVTN GITTERHKKK
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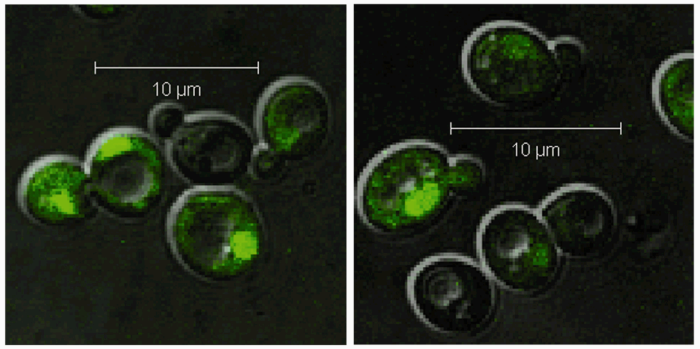
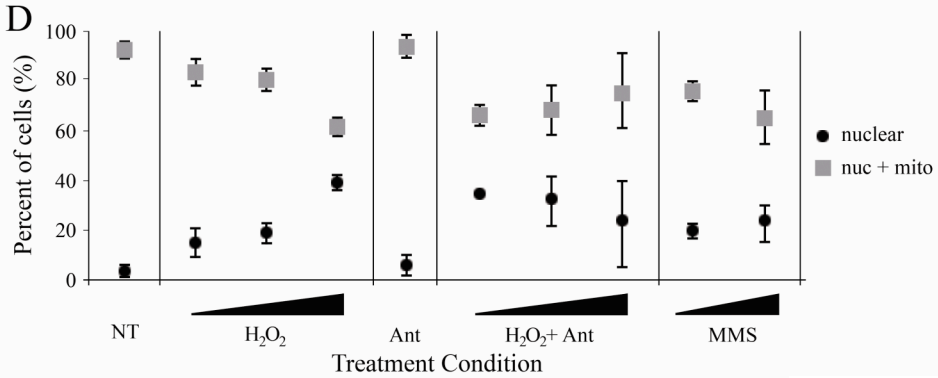
Nuclear localization of K364R Ntg1 is different from wild type

A

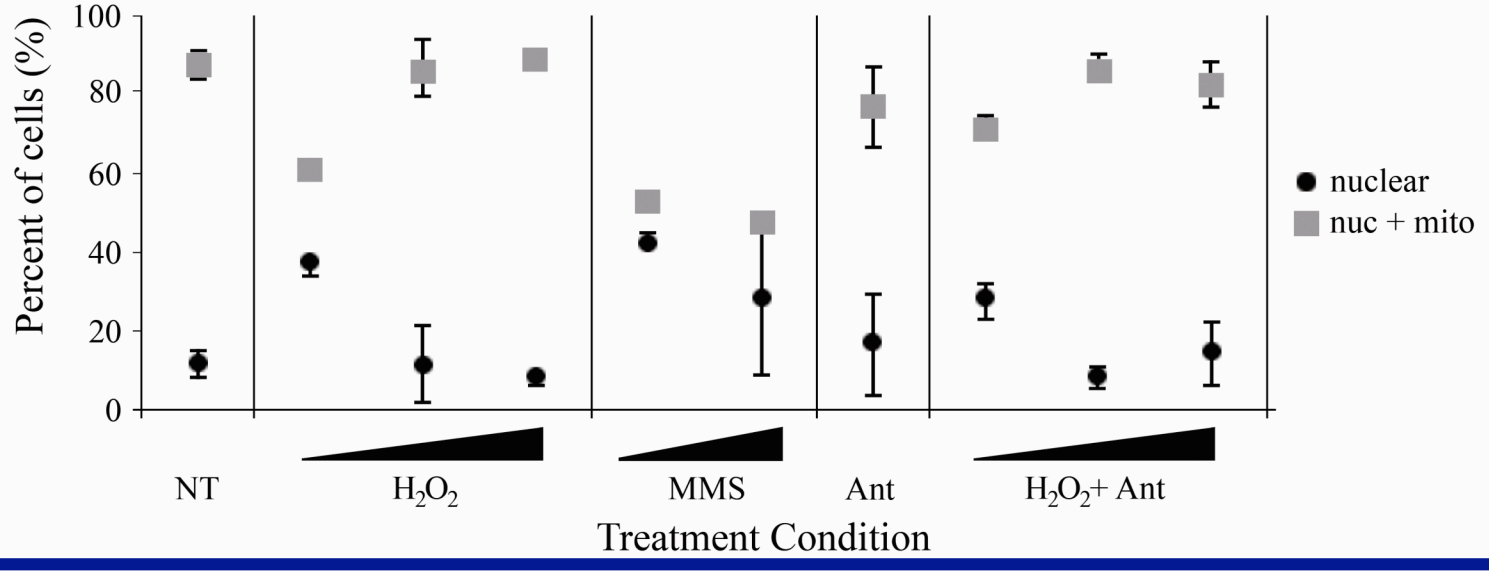
K364R Ntg1-GFP



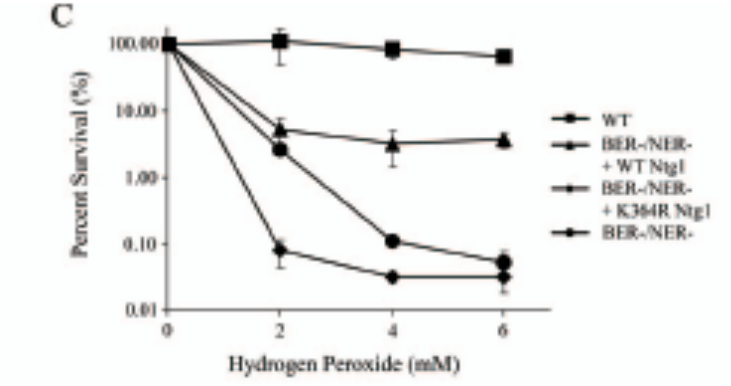


B

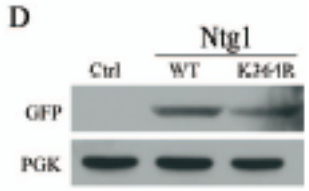
Ntg1 K364R Mutant

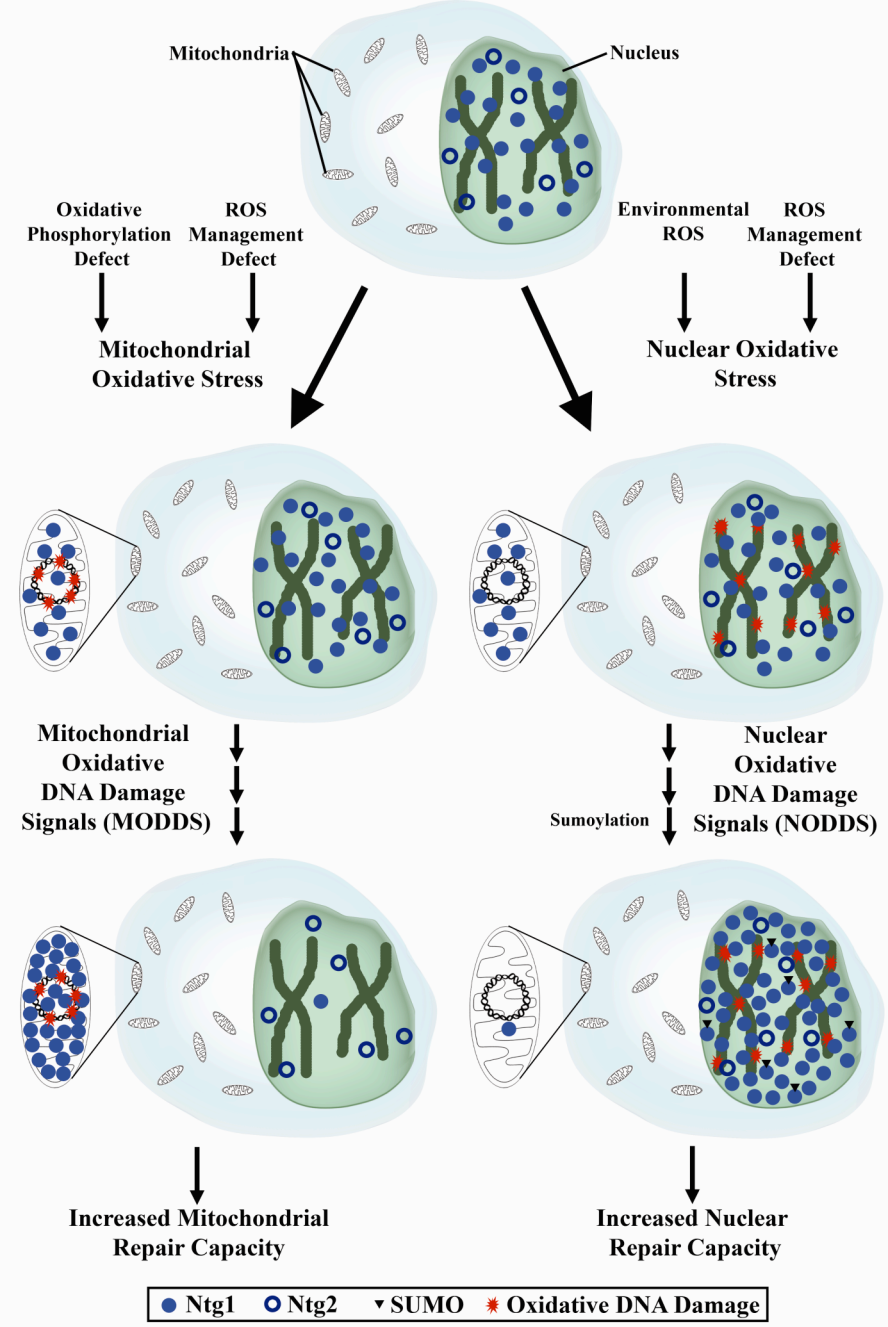


Sumoylation of Ntg1 K364 is important for repair of toxic DNA lesions



K364R mutant cannot reverse peroxide sensitivity





Model

- Localization of Ntg1 is nuclear and mitochondrial and Ntg2 is nuclear only.
- Localization of Ntg1 is influenced by oxidative stress; whereas, localization of Ntg2 is not influenced by oxidative stress.
- Mitochondrial localization of Ntg1 is DNA damage dependent, and we hypothesize that nuclear localization of Ntg1 is also DNA damage dependent.
- Ntg1 and Ntg2 are sumoylated.
- Sumoylation appears to influence the nuclear localization of Ntg1.
- K364R mutation of Ntg1 causes abnormal nuclear localization of Ntg1 in response to oxidative stress. Therefore, sumoylation may affect nuclear localization of Ntg1 during nuclear oxidative stress.

Amino Acid Sequence of Ntg1 and Ntg2

Putative NLS
Putative MTS
Catalytic domain
Putative active site lysine
Iron-sulfur center
Putative sumoylation sites

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301 HSLWYEINTV LVGFGQLICM ARGKRCDLCL ANDVCNARNE KLIESSKFHQ 350
351 LEDKEDIEKV YSHWLDTVTN GITTERHKKK
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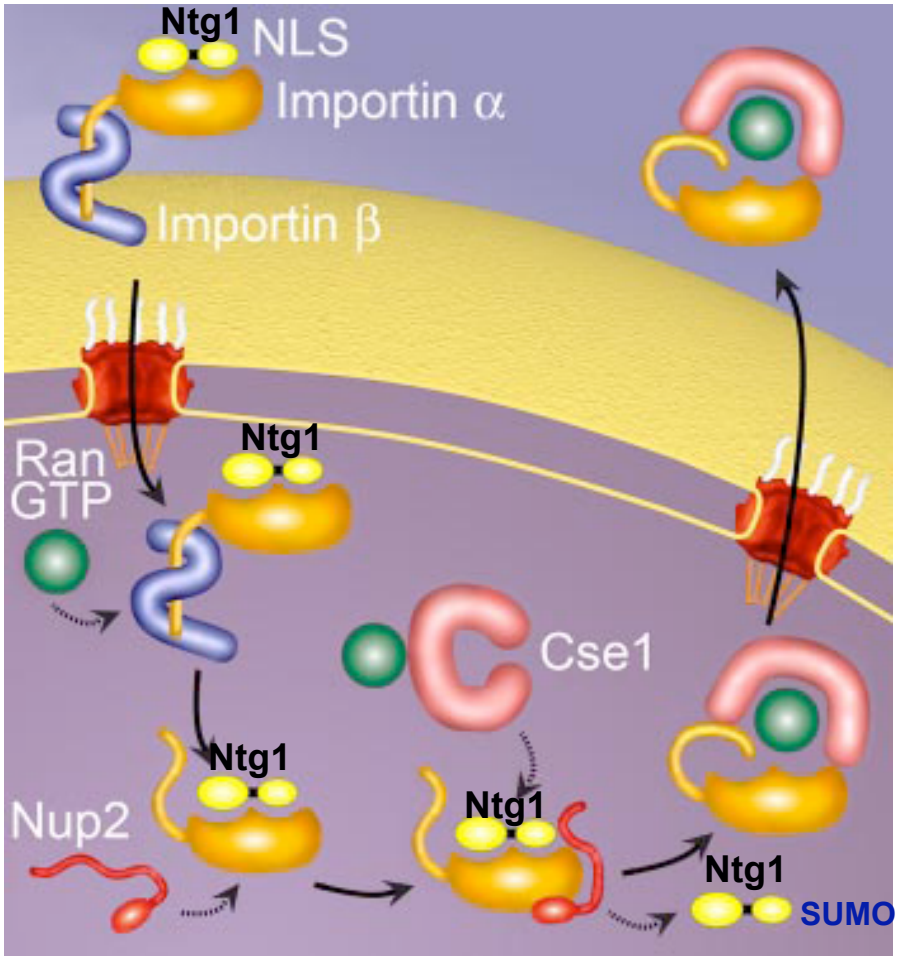
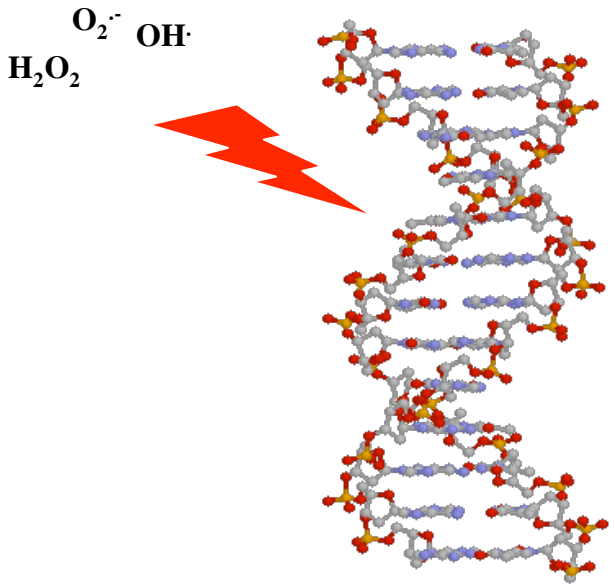
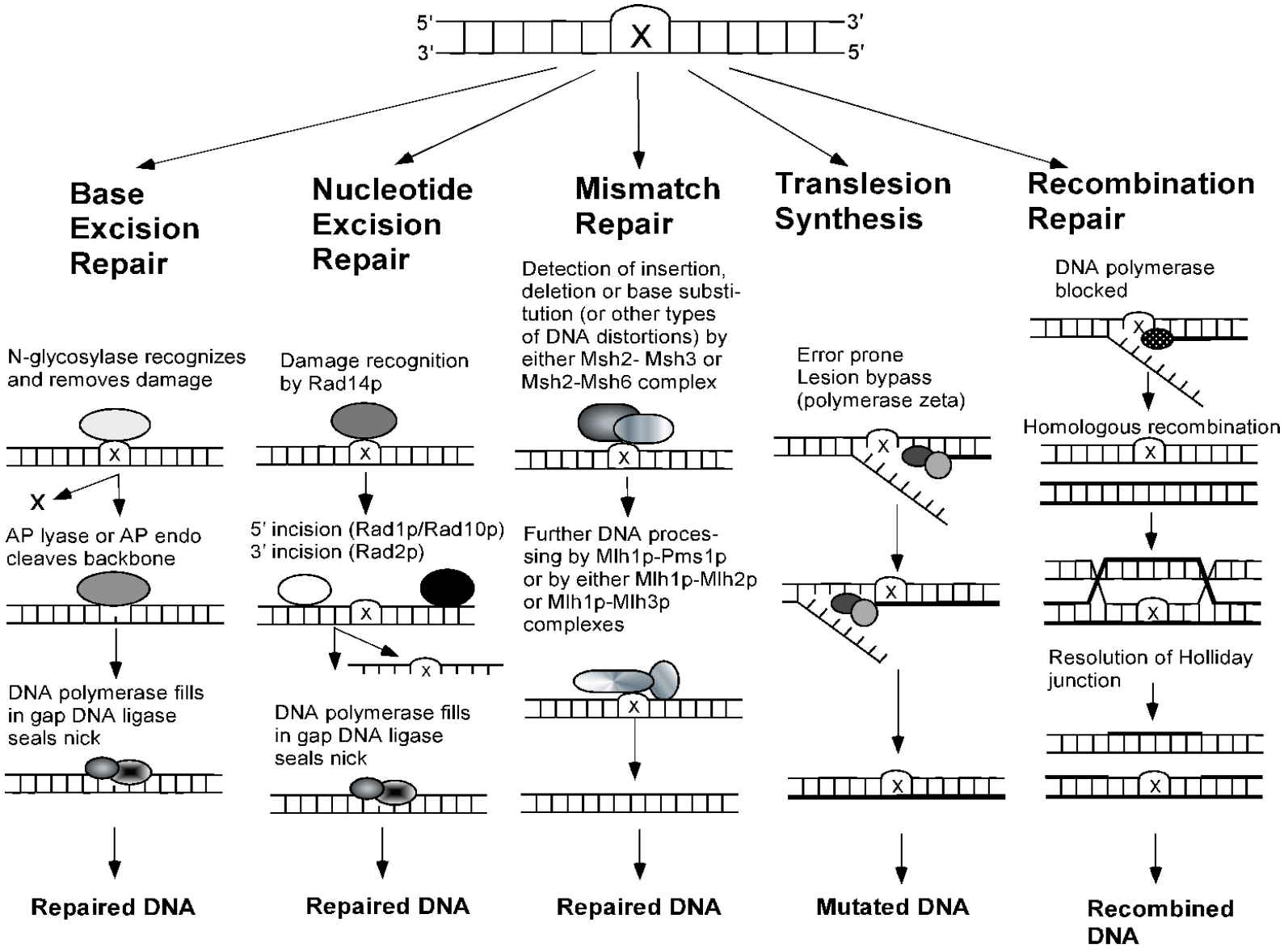
Nucleocytoplasmic Transport

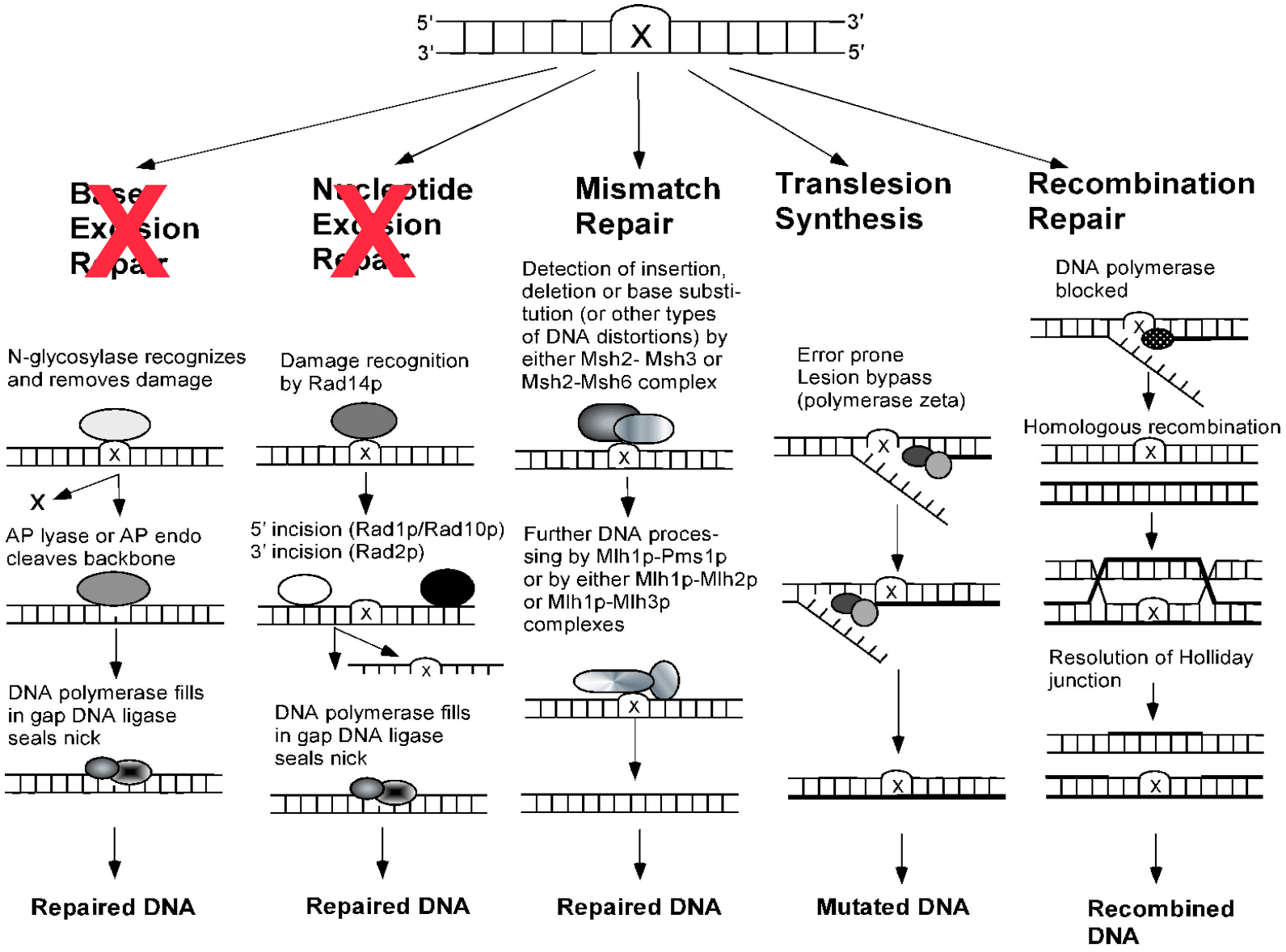
- NLS cargo binds to α/β import receptor
- Cargo is targeted to the nuclear pore through importin β receptor interactions with the nuclear pore
- Cargo is delivered into the nucleus – RanGTP binds to importin β to release α and NLS cargo



Genetic instability when DNA excision repair (BER and NER) pathways are corrupted or repair capacity is exceeded by amount of damage




5'
3'
X
3'
5'
Base Excision Repair
N-glycosylase recognizes and removes damage
X
AP lyase or AP endo cleaves backbone
DNA polymerase fills in gap DNA ligase seals nick
Repaired DNA
Nucleotide Excision Repair
Damage recognition by Rad14p
5' incision (Rad1p/Rad10p)
3' incision (Rad2p)
DNA polymerase fills in gap DNA ligase seals nick
Repaired DNA
Mismatch Repair
Detection of insertion, deletion or base substitution (or other types of DNA distortions) by either Msh2- Msh3 or Msh2-Msh6 complex
Further DNA processing by Mlh1p-Pms1p or by either Mlh1p-Mlh2p or Mlh1p-Mlh3p complexes
Repaired DNA
Translesion Synthesis
Error prone Lesion bypass (polymerase zeta)
Mutated DNA
Recombination Repair
DNA polymerase blocked
Homologous recombination
Resolution of Holliday junction
Recombined DNA


5'
3'
X
3'
5'
Base Excision Repair
Nucleotide Excision Repair
Mismatch Repair
Translesion Synthesis
Recombination Repair
N-glycosylase recognizes and removes damage
AP lyase or AP endo cleaves backbone
DNA polymerase fills in gap DNA ligase seals nick
Repaired DNA
Damage recognition by Rad14p
5' incision (Rad1p/Rad10p)
3' incision (Rad2p)
DNA polymerase fills in gap DNA ligase seals nick
Repaired DNA
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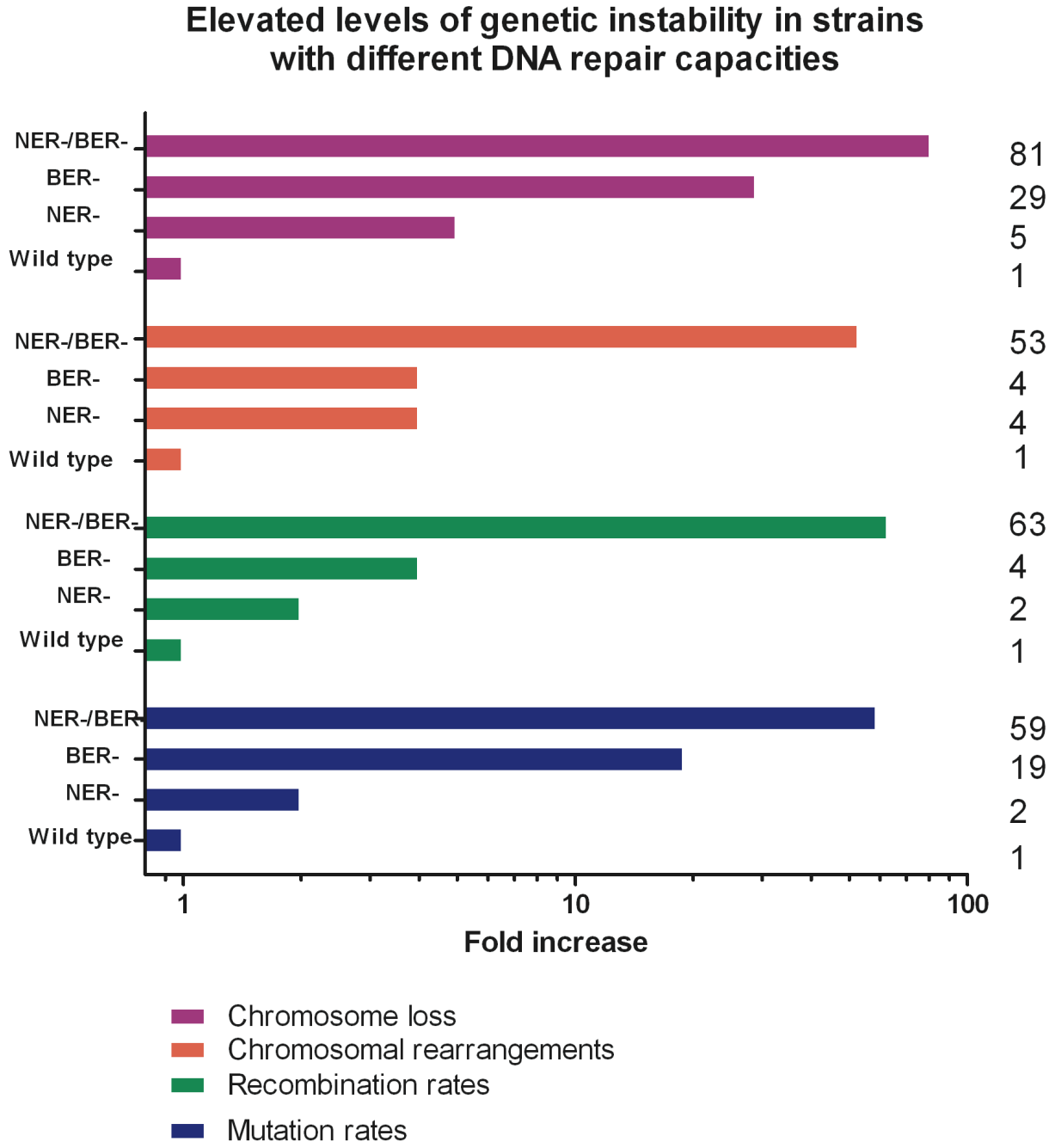

Elevated levels of genetic instability in strains with different DNA repair capacities
NER-/BER-
BER-
NER-
Wild type
81
29
5
1
NER-/BER-
BER-
NER-
Wild type
53
4
4
1
NER-/BER-
BER-
NER-
Wild type
63
4
2
1
NER-/BER-
BER-
NER-
Wild type
59
19
2
1
1
10
100
Fold increase
Chromosome loss
Chromosomal rearrangements
Recombination rates
Mutation rates

Frequencies are in the range of 10^{-5} to 10^{-9}

TABLE 3. Elevated levels of genetic instability in strains with different DNA excision repair capacities[a]

DNA repair background[b]	Mutation rate (10^{-7}) (95% confidence limits)	Recombination rate (10^{-5}) (95% confidence limits)	Arm loss (GCR) rate (10^{-9}) (95% confidence limits)	Chromosome loss rate (10^{-6}) (95% confidence limits)
Wild type	4.78 (2.18–5.98)	1.69 (1.19–7.32)	1.98 (0.24–7.13)	0.59 (0.33–0.97)
NER$^-$ (*rad1*)	8.45 [2] (7.37–11.1)	2.61 [2] (2.44–2.95)	8.00 [4] (3.84–14.7)	2.82 [5] (1.58–4.65)
BER$^-$ (*ntg1 ntg2 apn1*)	88.8 [19] (32.3–150)	6.80 [4] (4.83–12.5)	8.28 [4] (4.74–13.4)	17.2 [29] (0.74–33.8)
BER$^-$/NER$^-$ (*ntg1 ntg2 apn1 rad1*)	283 [59] (217–336)	107 [63] (99.7–108)	105 [53] (74.8–144)	47.9 [81] (26.2–80.4)

[a] Median rates for mutation, recombination, arm loss (GCR), and chromosome loss were determined for 10 to 20 cultures of two independent segregants of the same genotypes described in Materials and Methods. Increases (n-fold) in rates over those for the wild-type strain are indicated in brackets.
[b] The compromised DNA repair pathway in each strain type is shown; mutated genes are indicated in parentheses.

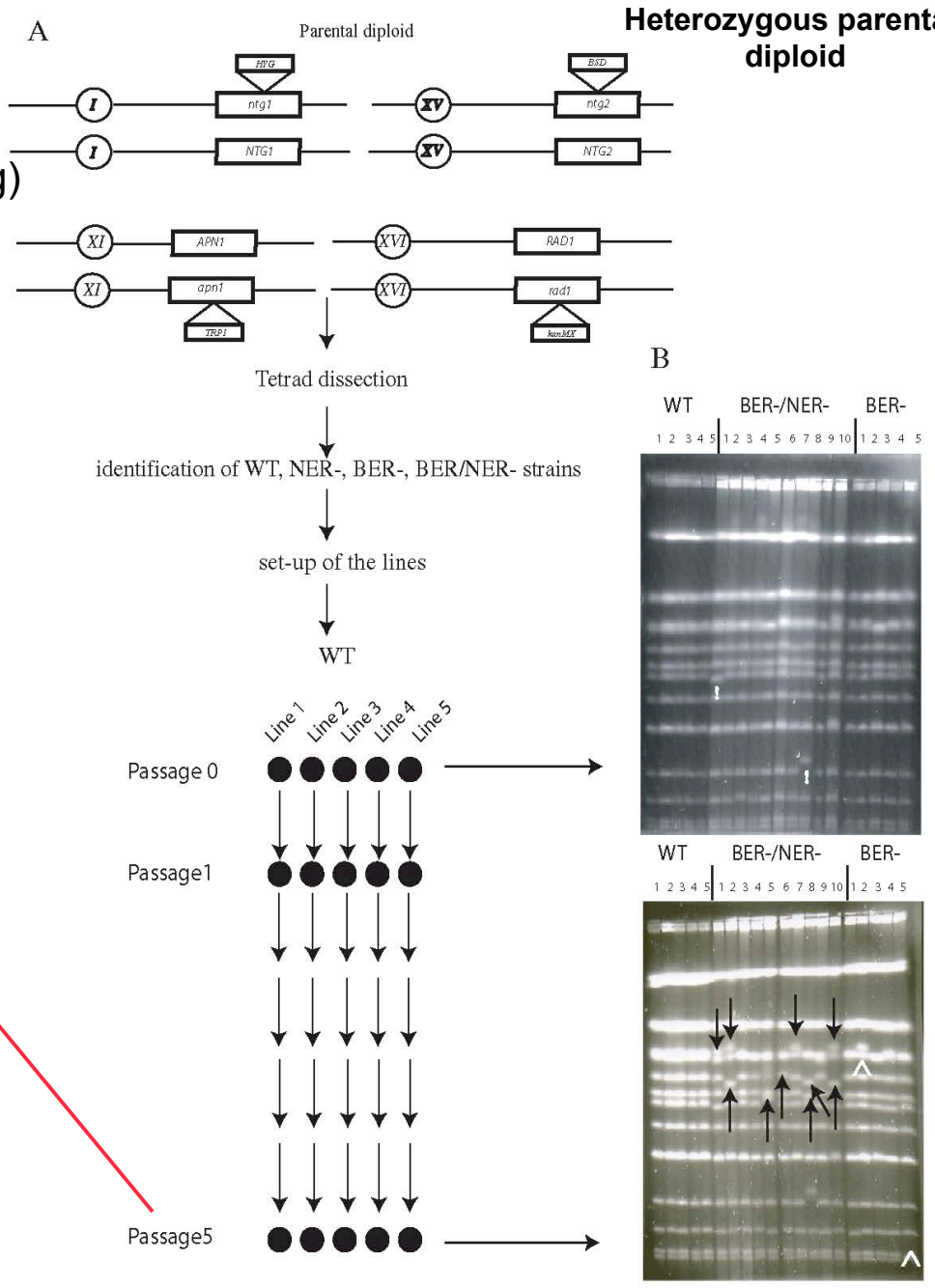
Selective conditions, low frequency events

CHEF gel analysis of entire chromosomes

Karyotype large scale aberrations in replicative aging haploid cell populations (compromised repair and ROS scavenging)

<u>Selective assays limitations:</u>
Low frequency events
Biological relevancy?

<u>Non-selective assay for CIN:</u>
"Evolution" of cells under persistent oxidative stress



Changes in size of chromosomes after 5 passages detected by CHEF gel analysis (~125 generations)

- Cells rapidly "evolve" CIN similar to evolution of increasingly genetically unstable clones of cancer cells
- Elevated levels of karyotypic changes in replicative aging yeast cells caused by persistent oxidative DNA damage
  - MMS (sub-toxic) chronic exposure causes similar result in WT cells

Frequencies are in the order of 10^{-3}!

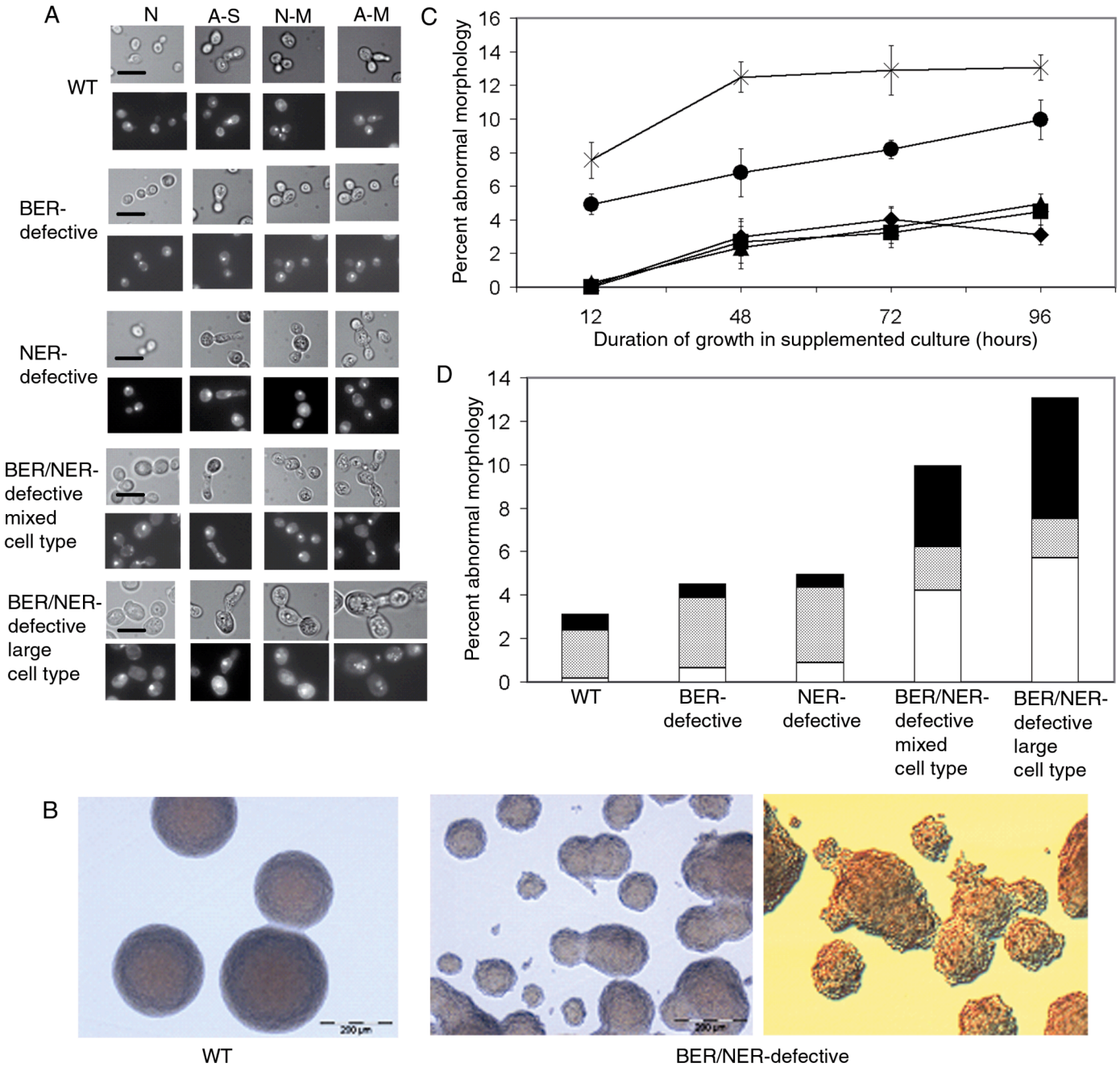
TABLE 5. Frequencies of large-scale chromosomal rearrangements in haploid strains with chronic, elevated levels of endogenous oxidative DNA damage

Strain description[a]	No. of rearrangements[b] (no. of lineages analyzed) after passage:				Total no. of rearrangements (total no. of lineages analyzed)	Estimated no. of rearrangements per cell division[c] (10^{-4})
	0	5	10	15		
Wild type	0 (10)	0 (10)	1 (10)	0 (10)	1 (30)	0.9
NER$^-$	0 (10)	1 (10)	1 (10)	1 (10)	3 (30)	2.7
BER$^-$	0 (10)	3 (10)	0 (10)	3 (10)	6 (30)	5.3
BER$^-$/NER$^-$	2 (20)	8 (20)	11 (19)	13 (19)	32 (58)	14.7
tsa1	0 (10)	3 (10)	4 (10)	0 (9)	7 (29)	6.4
NER$^-$ *tsa1*	0 (10)	3 (10)	3 (10)	1 (9)	7 (29)	6.4
BER$^-$ *tsa1*	3 (10)	3 (10)	5 (8)	1 (9)	9 (27)	8.9
BER$^-$/NER$^-$ *tsa1*	8 (20)	9 (20)	6 (20)	6 (16)	21 (56)	10.0

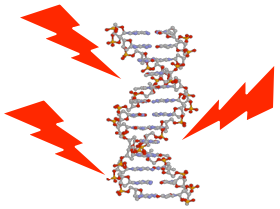
[a] Compromised DNA excision repair pathways and *TSA1* backgrounds are shown. The genes that were mutated to disable each DNA repair pathway are the same as those listed in Table 3.
[b] Number of lineages of the indicated genotype in which changes in the sizes of different chromosomes were detected by the separation of the genomic DNA by CHEF gel electrophoresis as described in Materials and Methods.
[c] The rates of rearrangements were calculated as described in the text (see Results).

Non-selective conditions, high frequency events

Have we evolved “cancer” in yeast?


A
N
A-S
N-M
A-M
WT
BER-
defective
NER-
defective
BER/NER-
defective
mixed
cell type
BER/NER-
defective
large
cell type
C
Percent abnormal morphology
0
2
4
6
8
10
12
14
16
12
48
72
96
Duration of growth in supplemented culture (hours)
D
Percent abnormal morphology
0
2
4
6
8
10
12
14
WT
BER-
defective
NER-
defective
BER/NER-
defective
mixed
cell type
BER/NER-
defective
large
cell type
B
WT
BER/NER-defective

DNA Damage-Induced ROS Signaling and Oxidative Stress



Damaged DNA

(cellular oxidases)

↑ROS

$O_2^{\cdot -}$

Yap1 Activation

(DNA Damage Responder)

Responses

(includes dynamic compartmentalization of DNA repair proteins)

DNA Repair

(NTG1, MAG1)

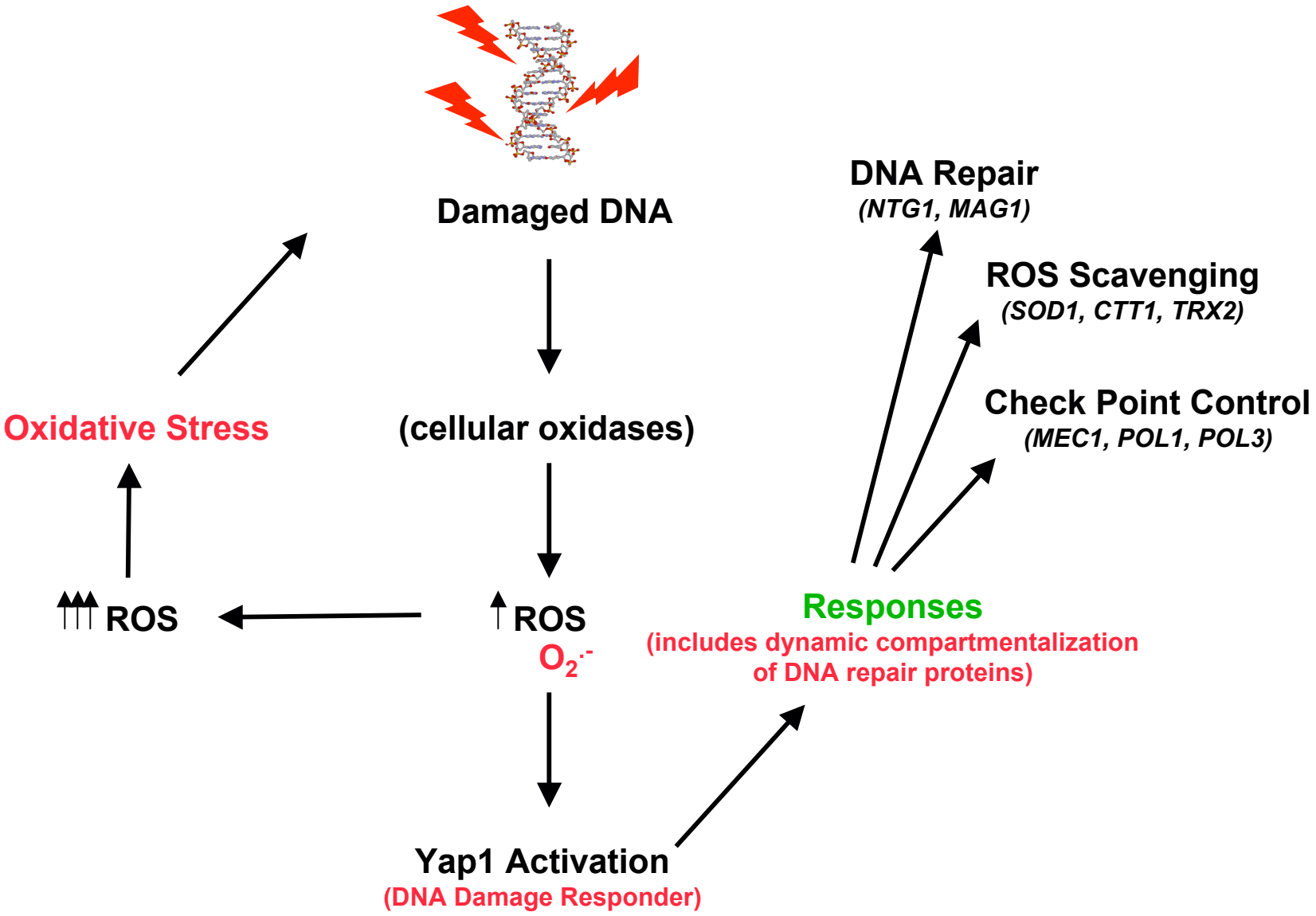
ROS Scavenging

(SOD1, CTT1, TRX2)

Check Point Control

(MEC1, POL1, POL3)

DNA Damage-Induced ROS Signaling and Oxidative Stress



DNA Damage-Induced ROS Signaling and Oxidative Stress

REC
TLS
Other

Chromosomal
Instability (CIN)

Damaged DNA

DNA Repair
(NTG1, MAG1)

ROS Scavenging
(SOD1, CTT1, TRX2)

Check Point Control
(MEC1, POL1, POL3)

Oxidative Stress

(cellular oxidases)

ROS

ROS
$O_2^{\cdot -}$

Responses
(includes dynamic compartmentalization
of DNA repair proteins)

Yap1 Activation
(DNA Damage Responder)

DNA Damage-Induced ROS Signaling and Oxidative Stress

REC
TLS
Other

Chromosomal
Instability (CIN)

Damaged DNA

DNA Repair
(NTG1, MAG1)

ROS Scavenging
(SOD1, CTT1, TRX2)

Check Point Control
(MEC1, POL1, POL3)

Oxidative Stress

(cellular oxidases)

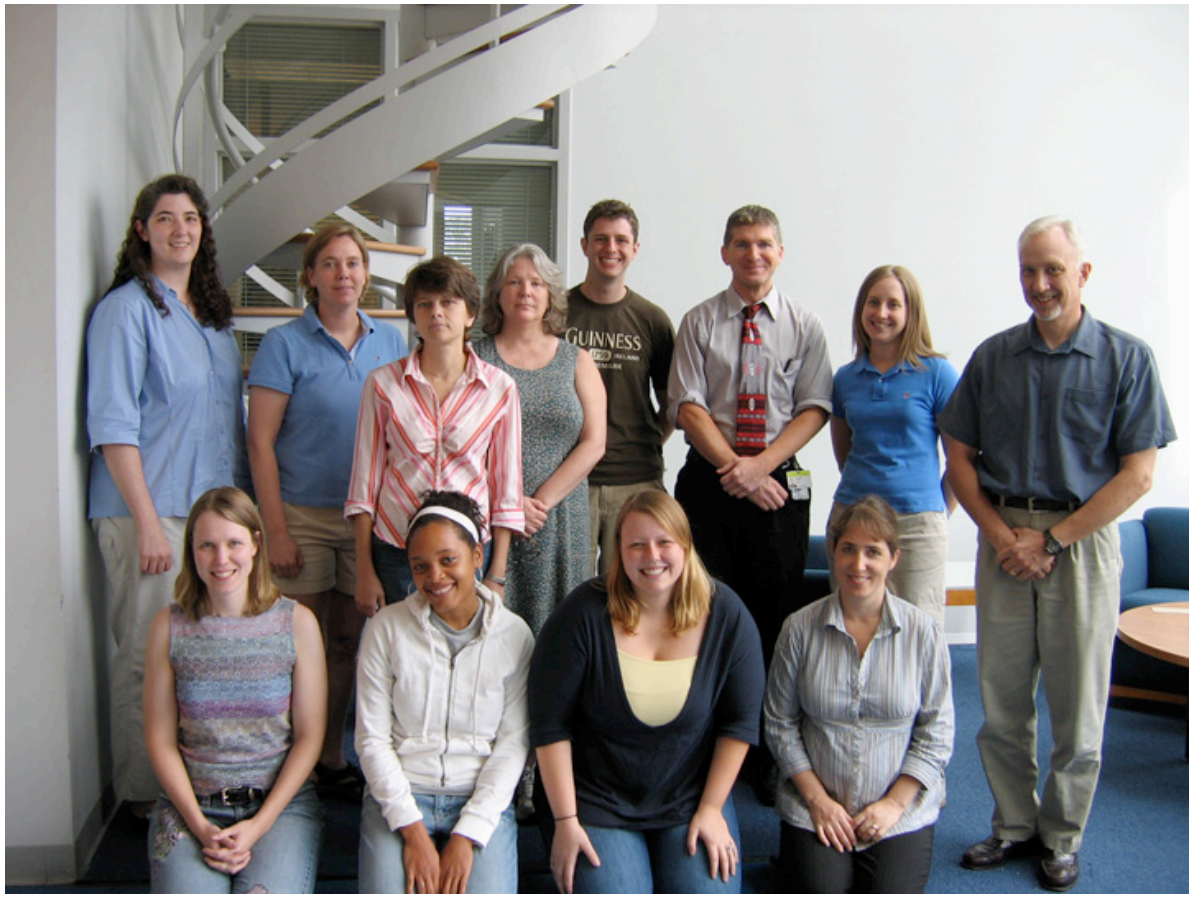
ROS

ROS
$O_2^{\cdot -}$

Responses
(includes dynamic compartmentalization
of DNA repair proteins)

Yap1 Activation
(DNA Damage Responder)

Colleagues, Collaborators, and Support



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Tina Saxowsky
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