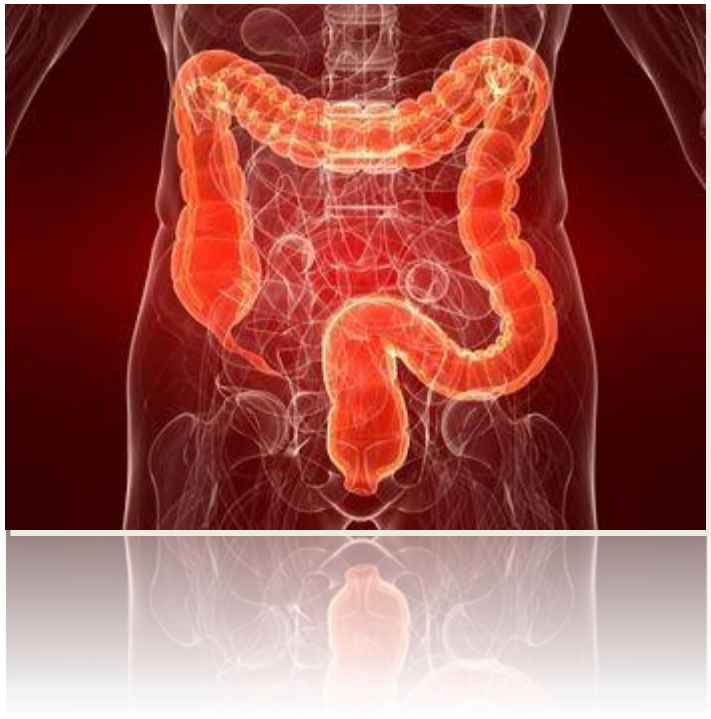
Inflammation and Cancer



Background

Stacey Lin

Lloyd Lab

Inflammation and Cancer

DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice

Meira et al., J. Clin. Invest. 188:2516-2525 (2008)

The Mutyh base excision repair gene influences the inflammatory response in a mouse model of ulcerative colitis

Casorelli et al., PloS One. 5(8):e12070 (2010)

http://en.wikipedia.org/wiki/Rudolf_Virchow

Rudolph Carl Virchow

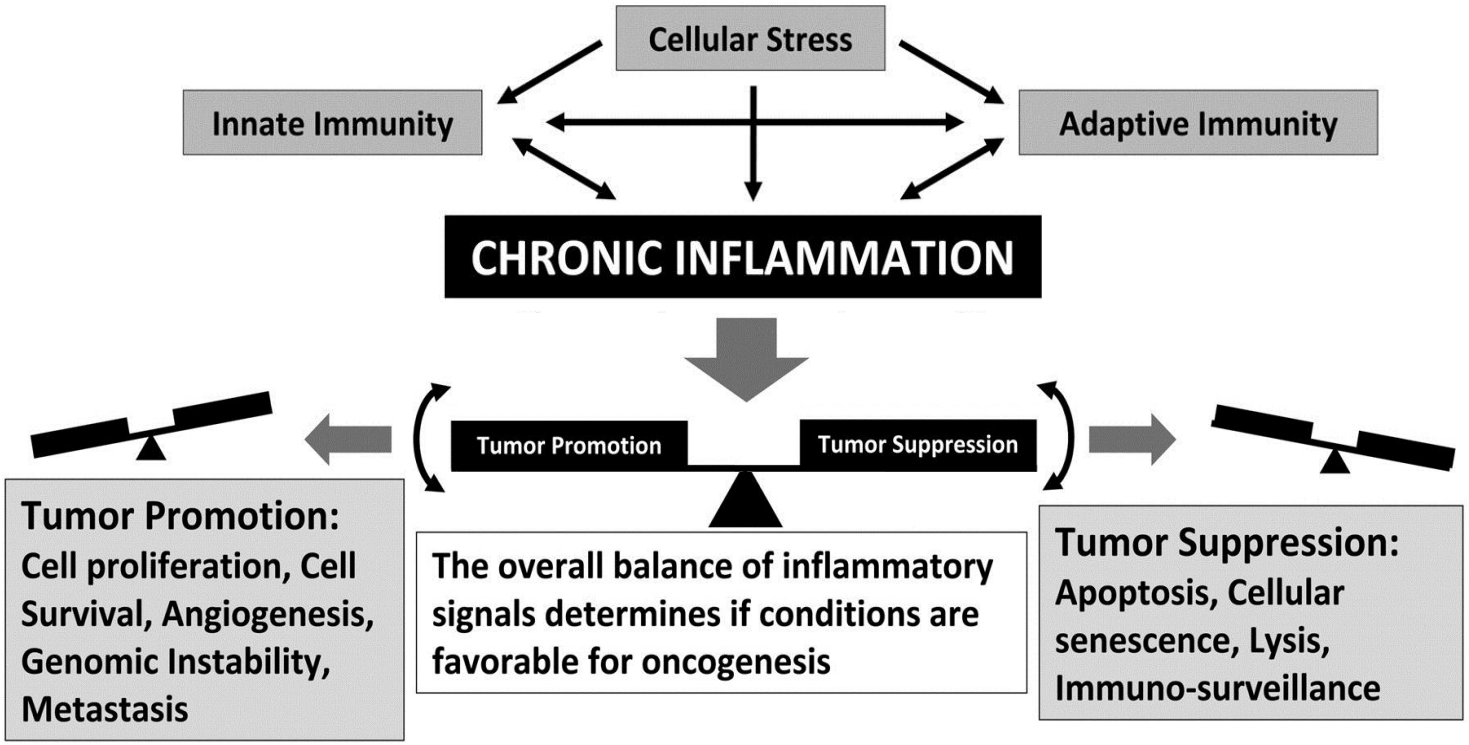
1821-1902, Father of Modern Pathology

Overview

- Inflammation and cancer
  - epidemiological association
  - molecular mediators
- Oxidative stress
- Base excision repair
  - unified model
  - highlight glycosylases

Inflammation & Cancer

- Acute inflammatory response usually beneficial
- Chronic inflammation can be oncogenic



Adapted from Schetter A J et al. Carcinogenesis 2009;31:37-49

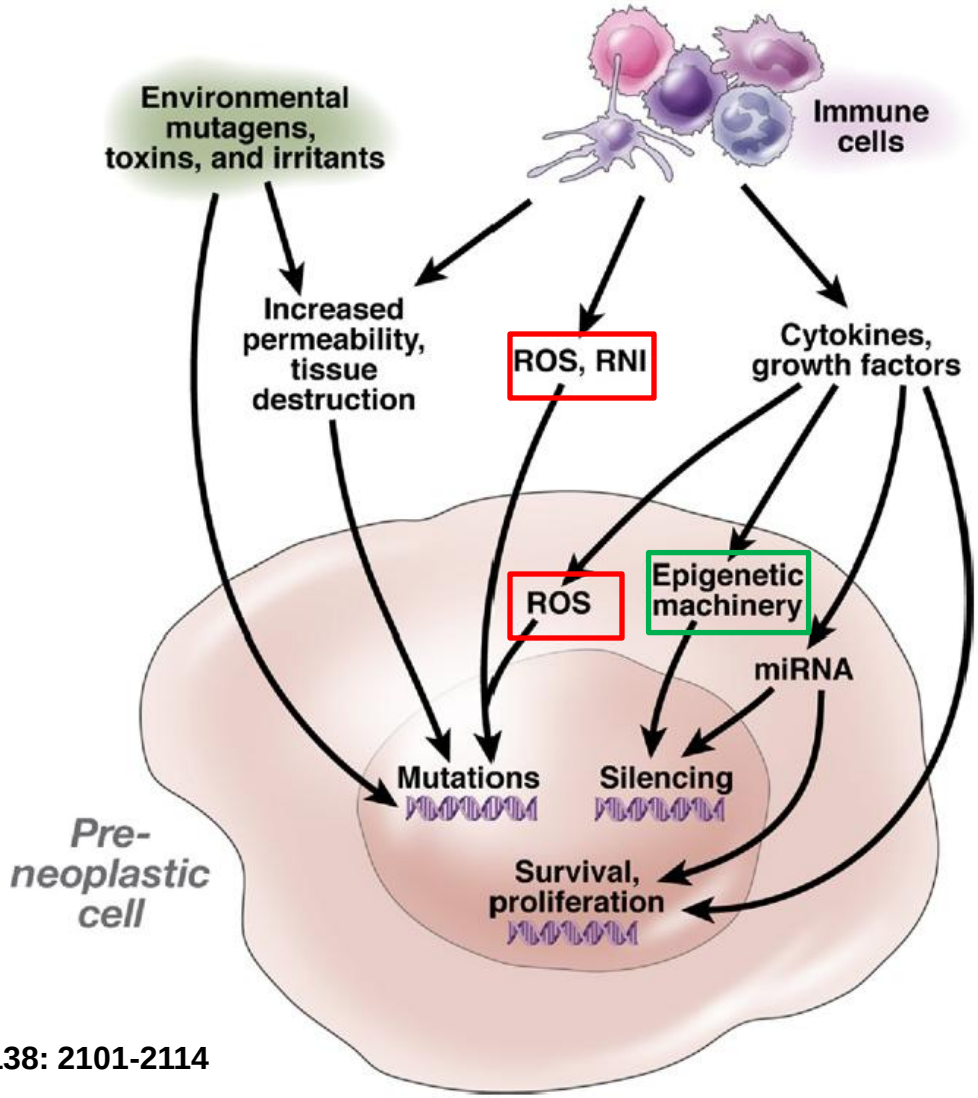
Chronic inflammation cause increased risk of Cancer development

Disease	Type of cancer	Increased risk
Auto-inflammatory/non-infectious		
Crohn's disease	Colon cancer	3
Ulcerative colitis	Colon cancer	6
Chronic pancreatitis	Pancreatic cancer	2–50
Hemochromatosis	Liver cancer	219
α-1-Anti-trypsin deficiency	Liver cancer	20
Acquired		
Viral		
Hepatitis B	Liver cancer	88
Hepatitis C	Liver cancer	30
Epstein–Barr virus	Hodkin's and Burkitt's	4
Bacterial		
Helicobacter Pylori	Gastric cancer	11
Pelvic inflammatory disease	Ovarian cancer	3
Chronic protatitis	Prostate cancer	2–3
Chemical/physical/metabolic		
Alcohol	Multiple cancers (including liver, pancreas, head and neck cancer)	2–7
Asbestos	Mesothelioma	>10
Obesity	Multiple cancers	1.3–6.5
Tobacco smoke and inhalation of other noxious chemicals	Lung cancer (and multiple other cancers)	>10
Gastric reflux, Barrett's esophagus	Esophageal cancer	50–100

Adapted from Schetter A J et al. Carcinogenesis 2009;31:37-49

Oncogenic mechanisms in chronic inflammation

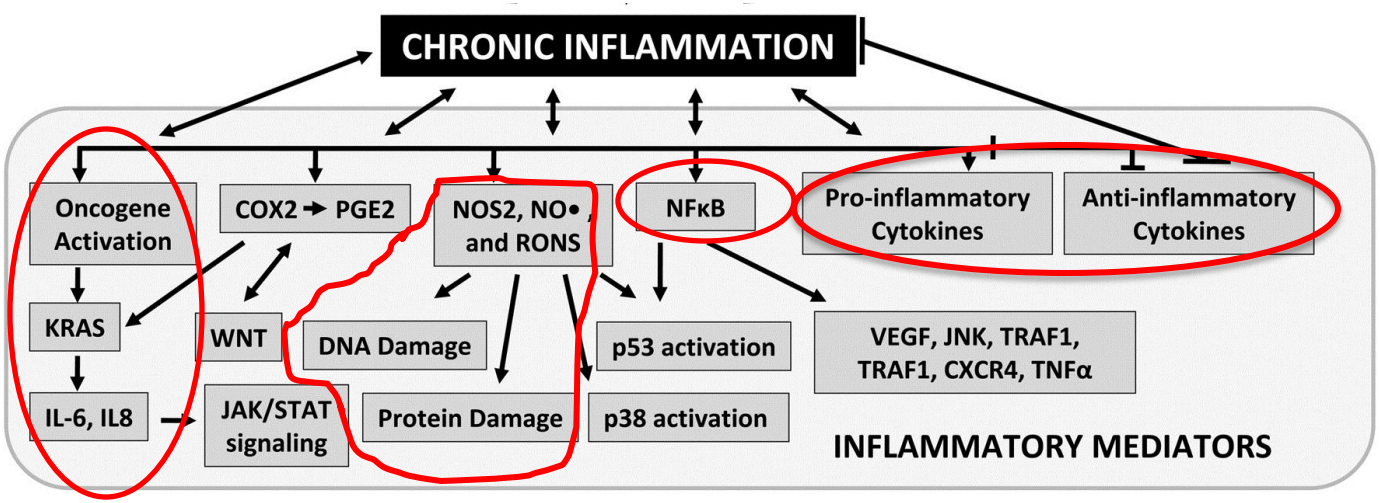
- Genomic instability
- Epigenetic alteration
- Cell survival
- Cell proliferation
- Angiogenesis
- Metastasis



Terzic et al. Gastroenterology 2010;138: 2101-2114

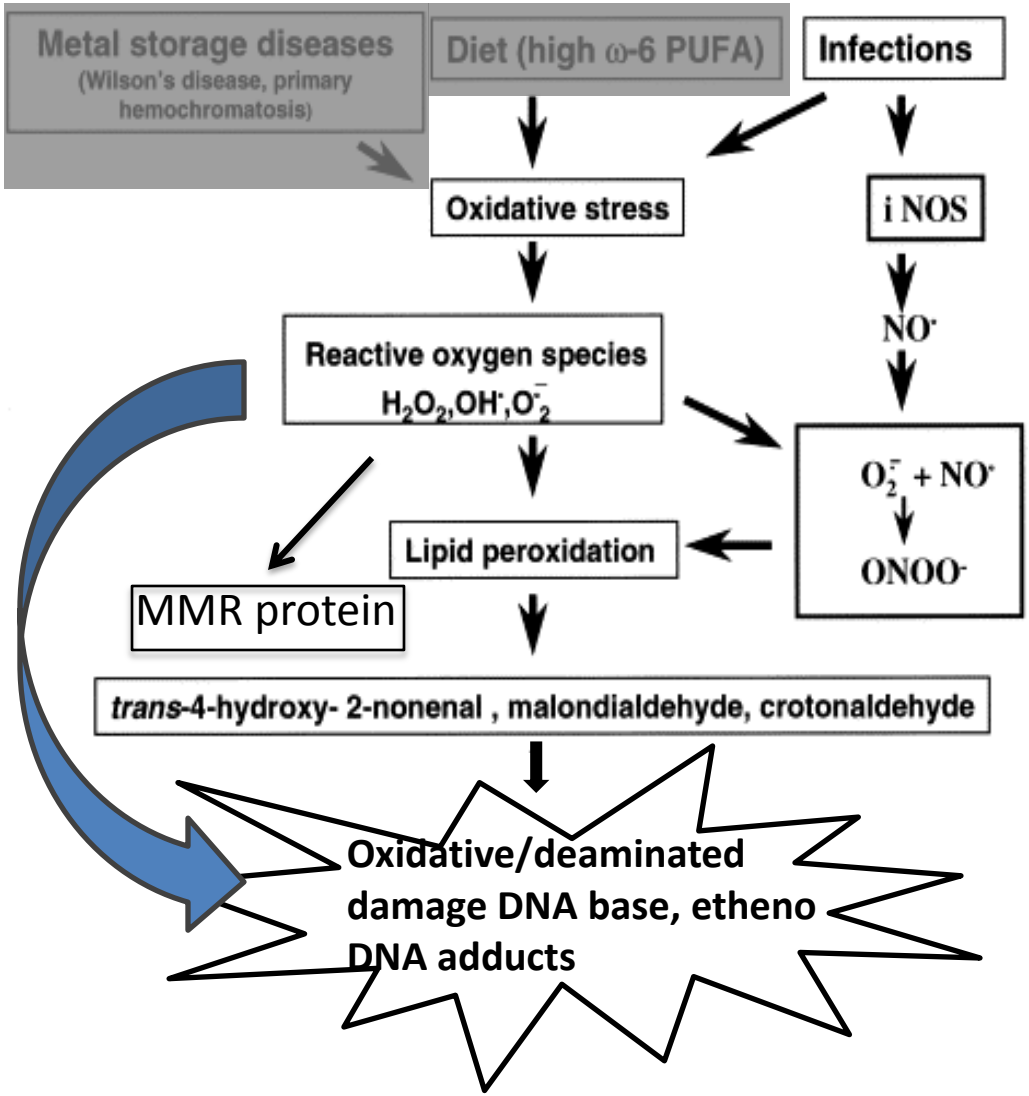
Common molecular mediators of inflammation and oncogenesis

- Extrinsic: induced by chronic inflammation and/or infection
- Intrinsic: caused by genetic alterations in oncogenes and/or tumor suppressor genes
- Main players: cytokines, chemokines, RONS, COX-2 and NFκB
- Pro-inflammatory cytokine: IL1, IL6, IL17, IL23 and TNFα
- Anti-inflammatory cytokine: IL10, IL13, TFGβ, IFNα



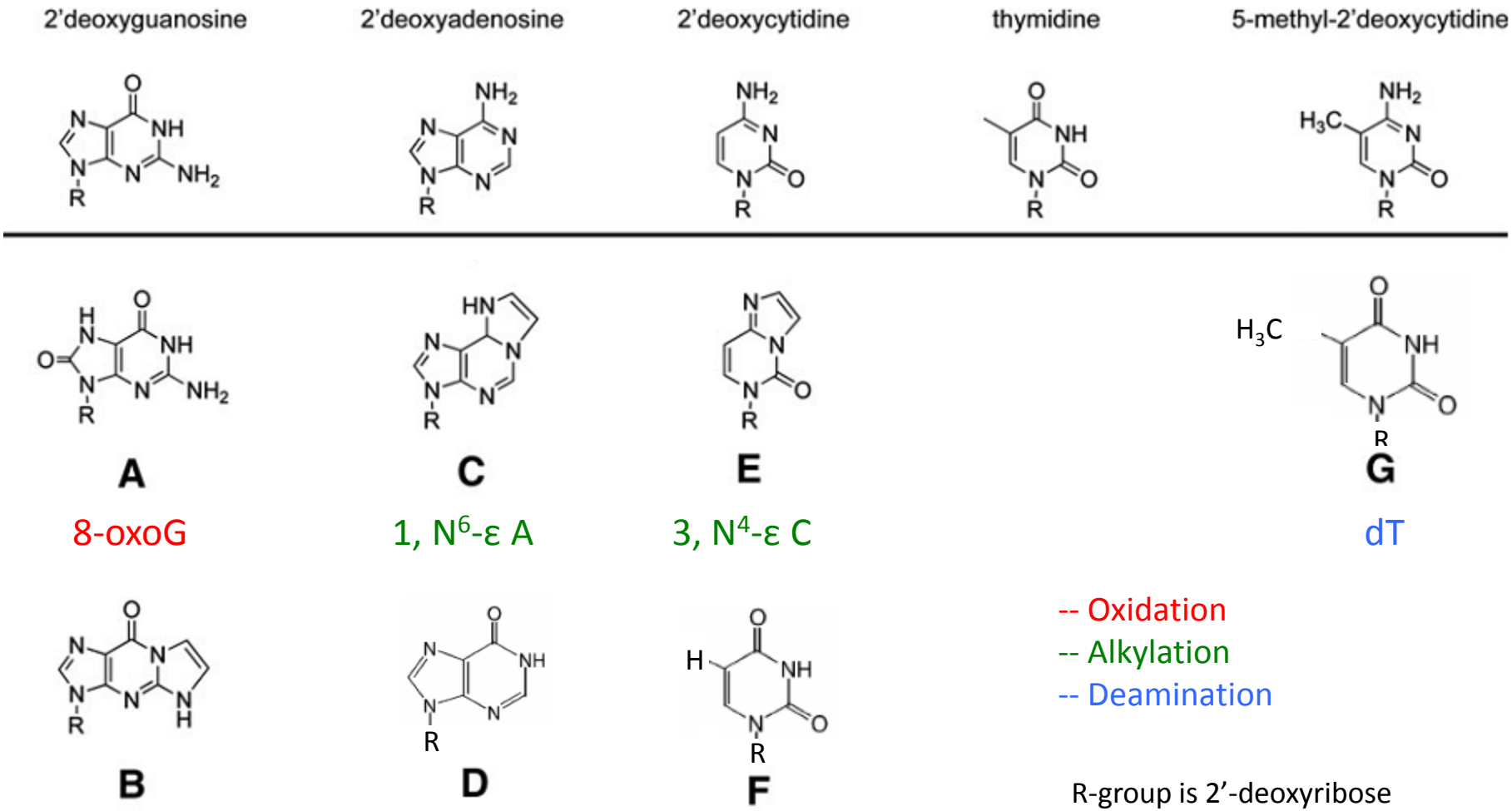
Adapted from Schetter A J et al. Carcinogenesis 2009;31:37-49

Protumorigenic effects of RONS



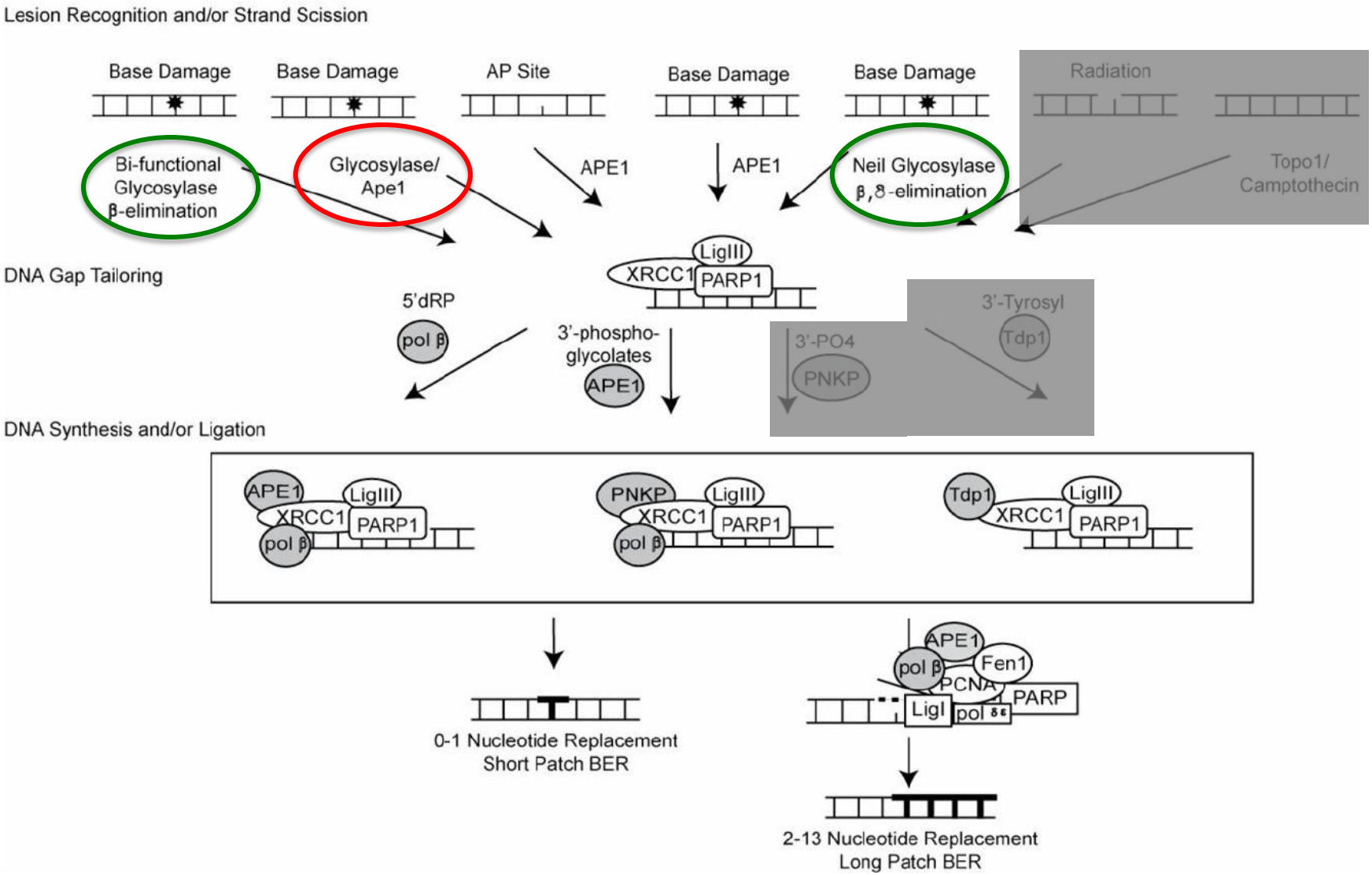
Adapted from Jagadeesan Naira et al., Mutation research 424, 59–69 (1999)

RONS-induced DNA damage (base oxidation, deamination, alkylation by LPO)



Adapted from Svilar et al., Antioxid Redox Signal. 14:2491-507 (2010)

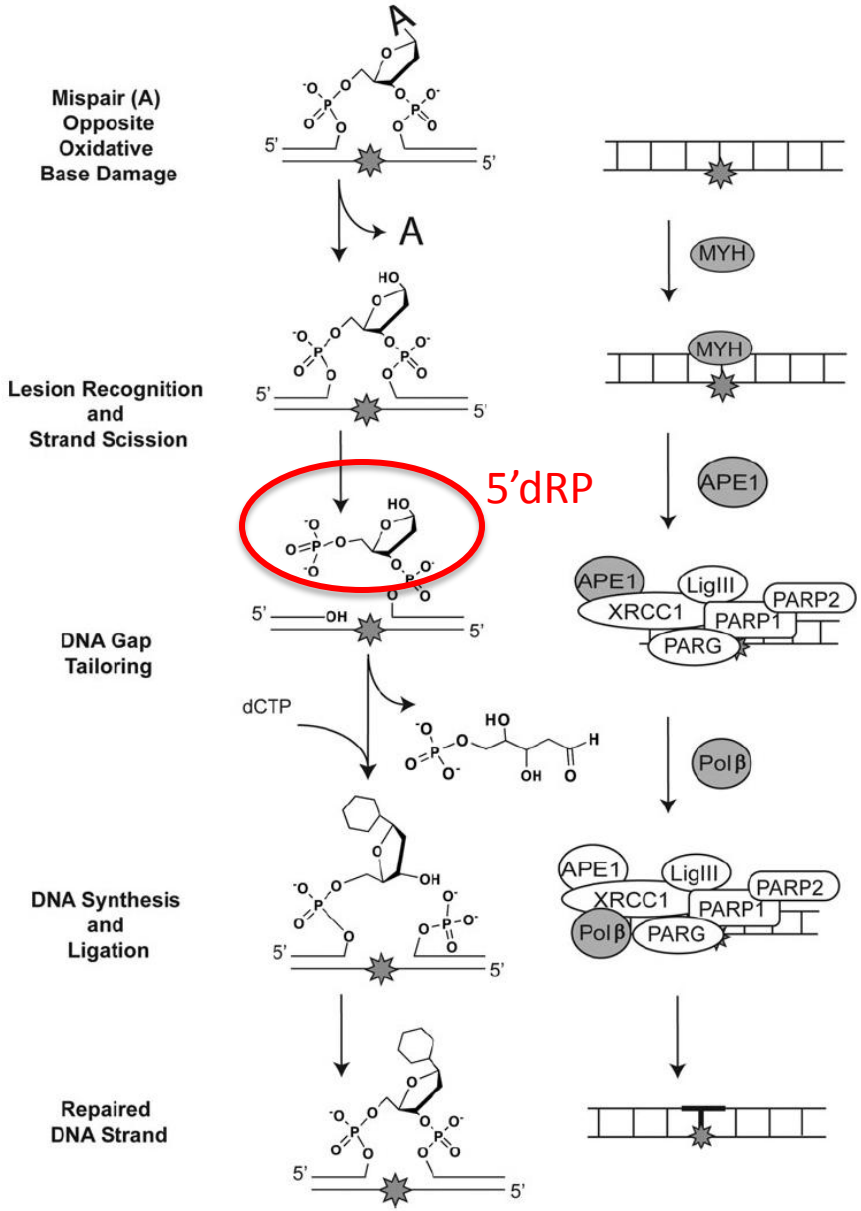
Base excision repair (BER) pathway



Almeida KH and Sobol RW. DNA repair 6:695-711 (2007)

MUTYH (*E. coli* MutY homolog) initiated BER pathway

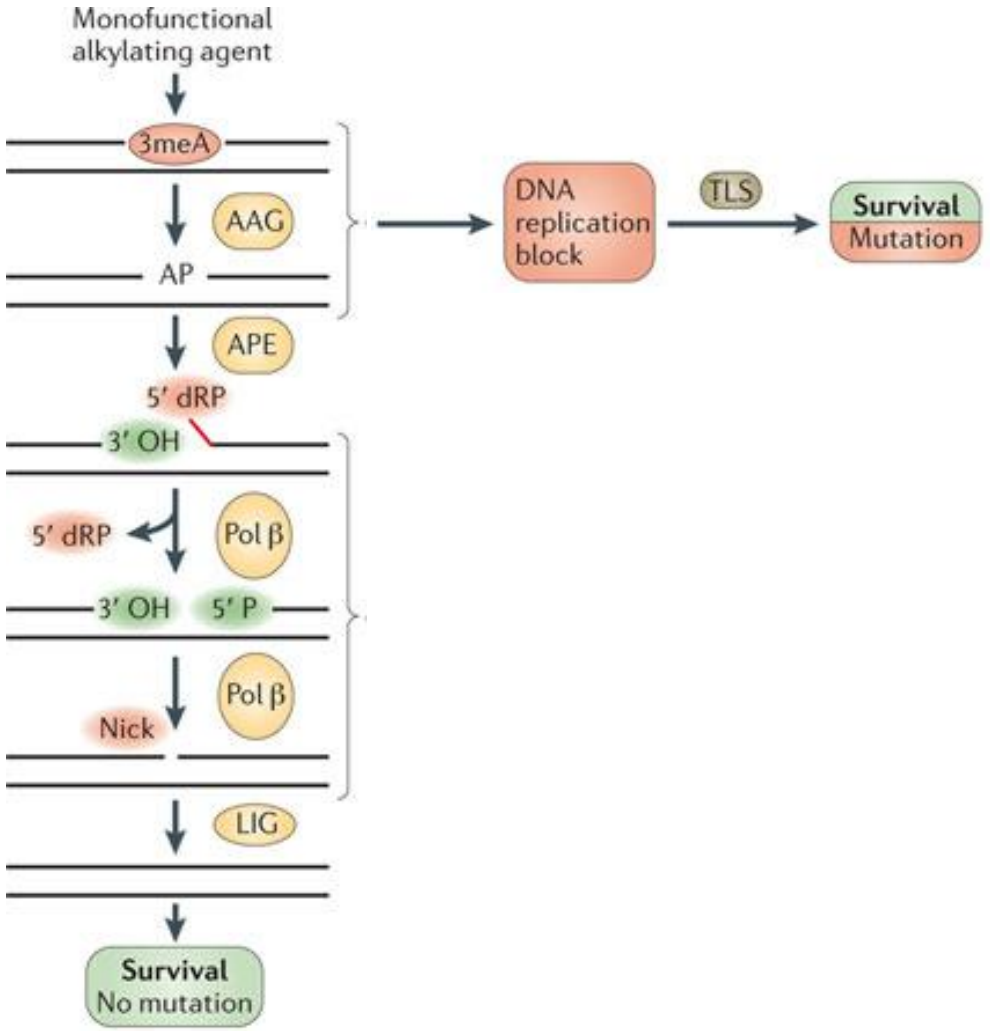
- Remove A from 8-oxoG:A mispairs to prevent G->T transversion
- MUTYH deficiency in mouse enhances spontaneous and oxidative stress-induced intestinal tumors
- inherited defects in MUTYH in patients cause multiple colorectal adenoma and carcinoma
- 8-oxoG accumulation accompanied by MUTYH expression pattern alters in UC-associated neoplasia



Svilar et al., Antioxid Redox Signal. 14:2491-507 (2010)

AAG (Alkyladenine DNA glycosylase) initiated BER pathway

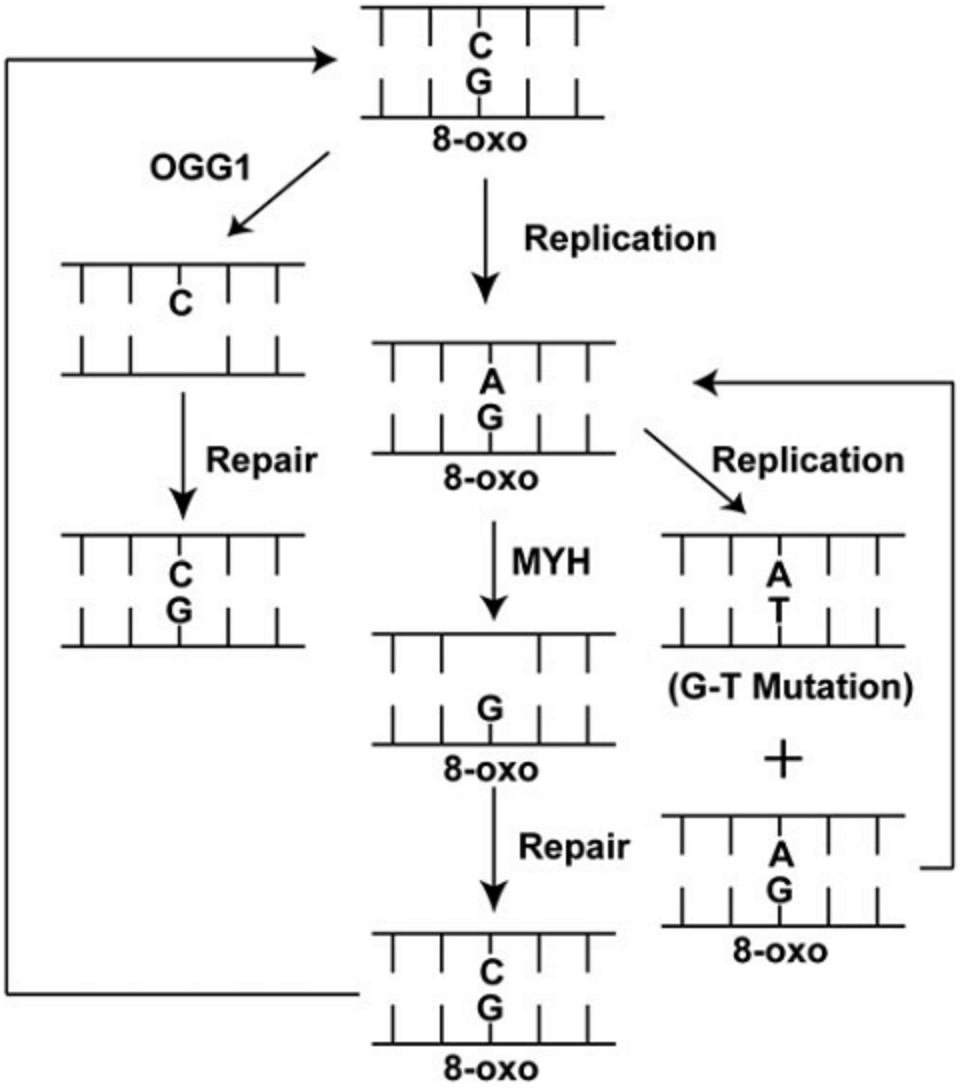
- Major DNA substrate: 3-meA, 7-meG, hypoxanthine (Hx), and 1,N^6-εA and 1, N^2-ε G
- Enhanced AAG expression in response to increase DNA damage in inflamed UC tissues
- Aag-null mice has higher colon cancer frequency induced by methylating agent (AOM)



Fu et al., Nature Reviews Cancer 12, 104-120 (2012)

Consequence of BER repair defect

- Mutation caused by translesion synthesis in replication
- Genome instability



Questions

How does elevated RONS-induced DNA damage lead to inflammation-associated tumorigenesis?

- How does the DNA damage response (DDR) operate in this inflammatory cell context?

- What role does DNA repair (BER) play in inflmmation-induced carcinogenesis?

- Can the excised damaged base or residual damaged base serve as signal molecules?