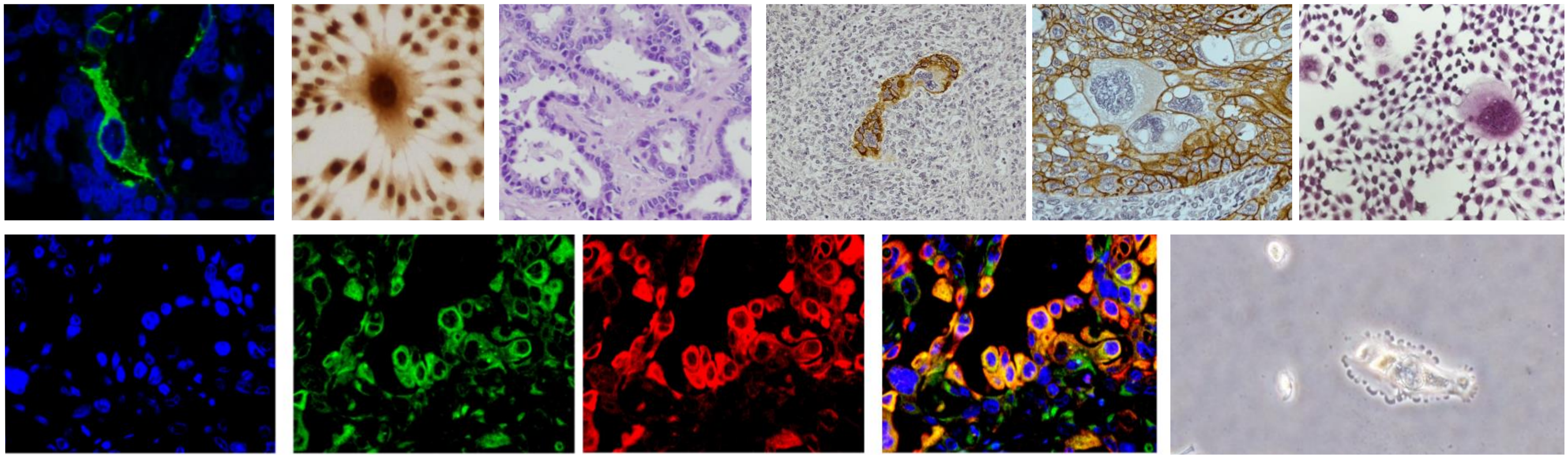
Oxidative Stress



Raynoo Thanan, PhD. (Medical Biochemistry)
Raynoo@kku.ac.th

MD637702, 14th Feb 2025, 10 a.m.–12 p.m.

Before coming to this session,
students should review the following items

- ☐ Chemistry of biomolecules
  - -Chemistry of lipid
  - -Chemistry of protein
  - -Chemistry of carbohydrate
  - -Chemistry of nucleic acid

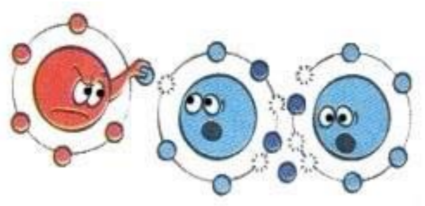
- ☐ Metabolism of biomolecules
  - -Metabolism of lipid
  - -Metabolism of protein
  - -Metabolism of carbohydrate
  - -Metabolism of nucleic acid

Outline

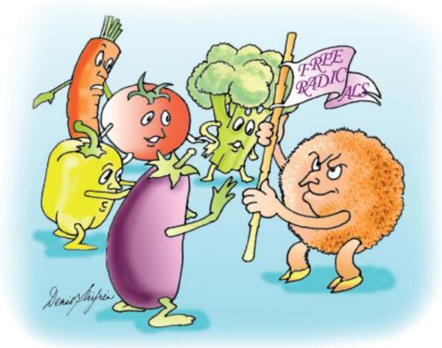
1. Definitions of oxidants and antioxidants
2. Types of oxidants
3. Types of antioxidants
4. Definition of oxidative stress
5. Consequences of oxidative stress
    - 5.1 Adaptation
    - 5.2 Damage (lipid, protein, DNA)
    - 5.3 Mutation & epigenetic change
    - 5.4 Repair
    - 5.5 Senescence
    - 5.6 Death
6. Oxidative stress related diseases

Definitions of oxidants and antioxidants

Oxidants are reactants that oxidize or remove electrons from other reactants during a redox reaction.



Antioxidants are substances that can prevent or slow damage to cells caused by oxidants.



Types of oxidants

Reactive Oxygen Species (ROS)

Radicals:

$O_2^{\cdot -}$	Superoxide
$OH^{\cdot}$	Hydroxyl
$RO_2^{\cdot}$	Peroxyl
$RO^{\cdot}$	Alkoxyl
$HO_2^{\cdot}$	Hydroperoxyl

Non-Radicals:

H_2O_2	Hydrogen peroxide
$HOCl^-$	Hypochlorous acid
O_3	Ozone
$^1O_2$	Singlet oxygen
$ONOO^-$	Peroxynitrite

Reactive Nitrogen Species (RNS)

Radicals:

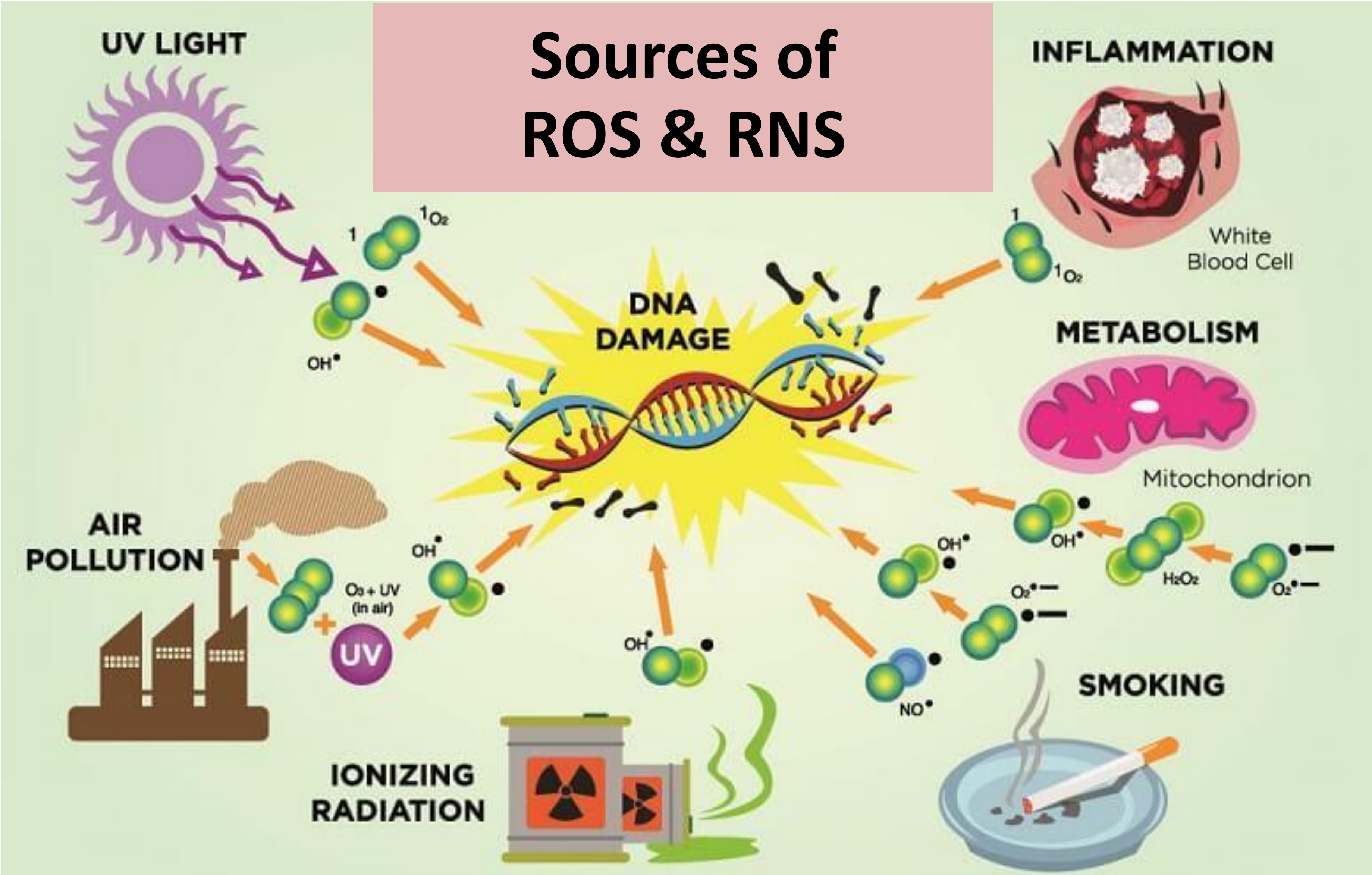
$NO^{\cdot}$	Nitric Oxide
$NO_2^{\cdot}$	Nitrogen dioxide

Non-Radicals:

$ONOO^-$	Peroxynitrite
ROONO	Alkyl peroxynitrites
N_2O_3	Dinitrogen trioxide
N_2O_4	Dinitrogen tetroxide
HNO_2	Nitrous acid
NO_2^+	Nitronium anion
NO^-	Nitroxyl anion
NO^+	Nitrosyl cation
NO_2Cl	Nitryl chloride

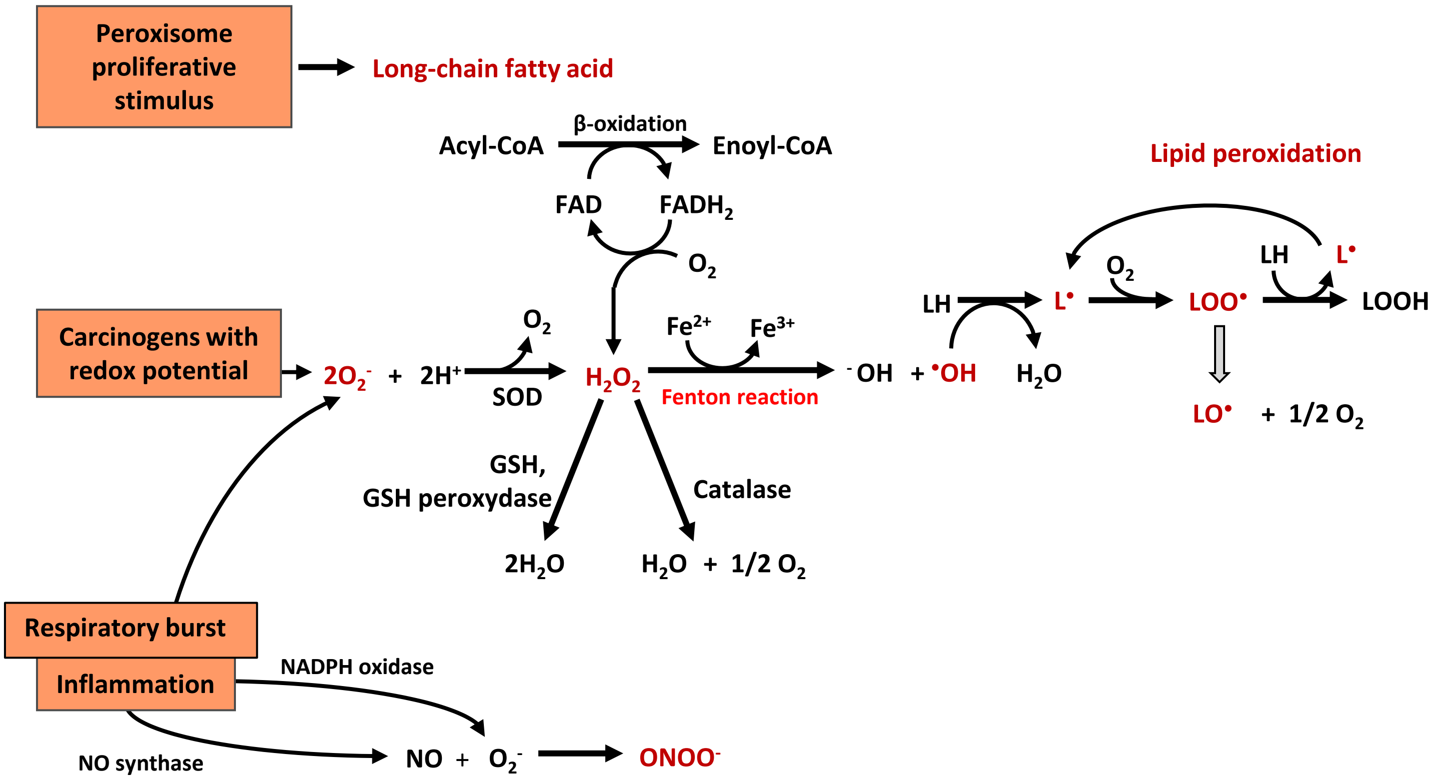
https://www.semanticscholar.org/

Sources of ROS & RNS



https://biologydictionary.net/oxidative-stress/

ROS and RNS generation in body



Thanan R et al., Int J Mol Sci.2015

Types of antioxidants

ANTIOXIDANT PROTECTION SYSTEM IN HUMANS

Endogenous antioxidants

- Bilirubin
- Enzymes:
  - copper/zinc and manganese-dependent superoxide dismutase (SOD)
  - iron-dependent catalase
  - selenium-dependent glutathione peroxidase
- NADPH and NADH
- Thiols, e.g. glutathione, lipoic acid, *N*-acetyl cysteine
- Ubiquinone (coenzymeQ10)
- Uric acid

Dietary antioxidants

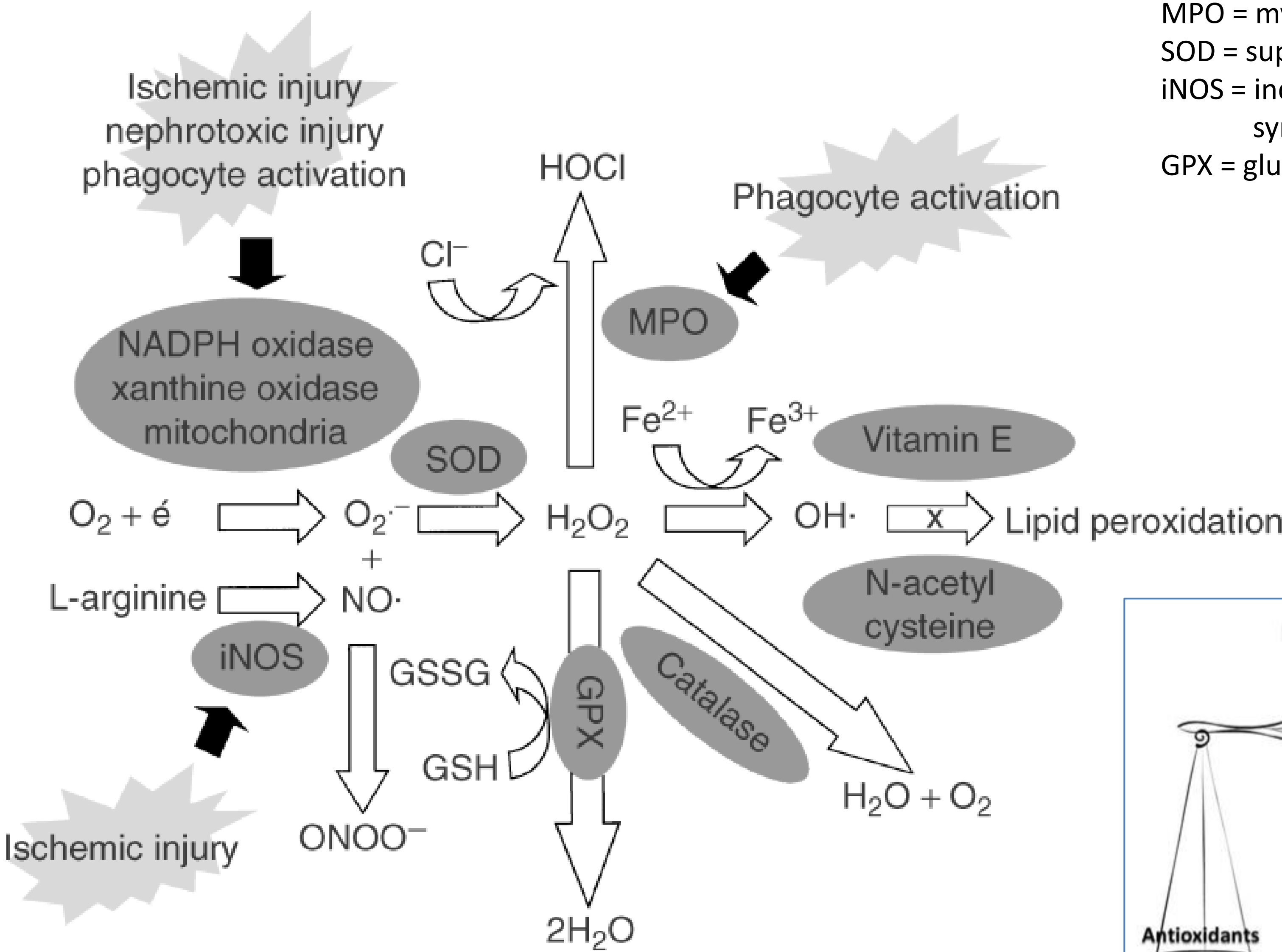
- Vitamin C
- Vitamin E
- β-Carotene and other carotenoids and oxycarotenoids, e.g. lycopene and lutein
- Polyphenols, e.g. flavonoids, flavones, flavonols and proanthocyanidins

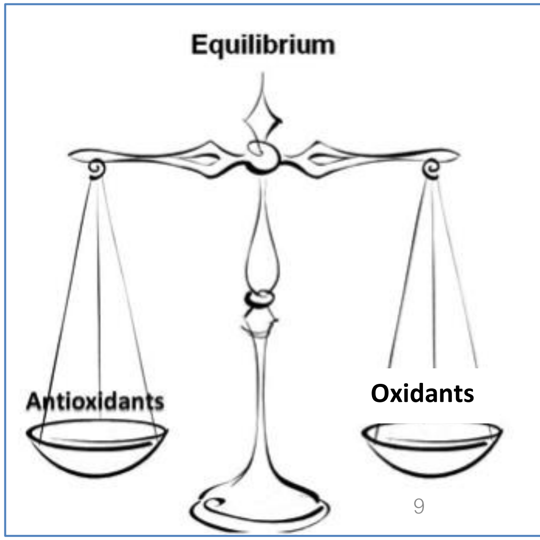
Metal binding proteins

- Albumin(copper)
- Ceruloplasmin(copper)
- Metallothionein(copper)
- Ferritin(iron)
- Myoglobin(iron)
- Transferrin(iron)

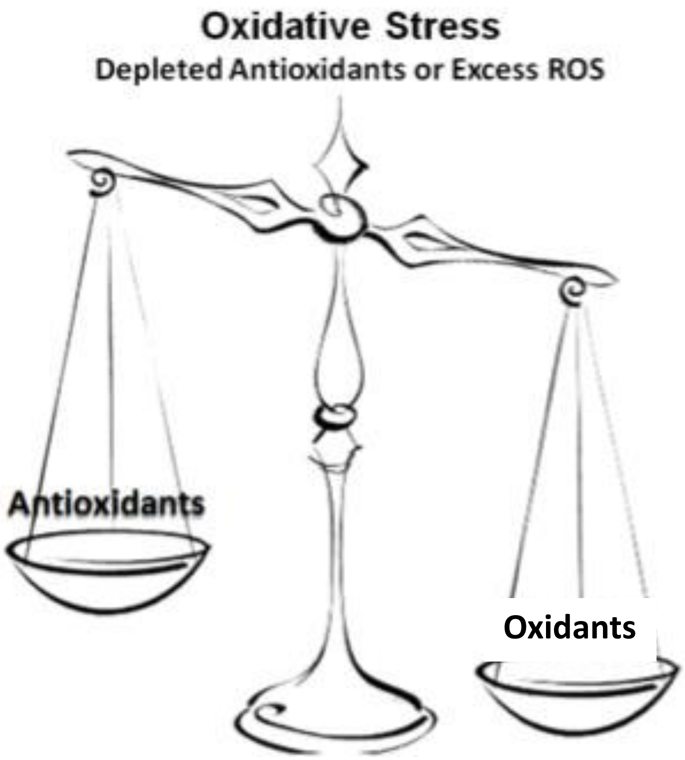
Oxidants vs Antioxidants

MPO = myeloperoxidase
SOD = superoxide dismutase
iNOS = inducible nitric oxide synthase
GPX = glutathione peroxidase





Definition of oxidative stress



Oxidative stress is an imbalance between oxidant and antioxidant systems that results in a large abundance of oxidants rather than antioxidants.

Outline

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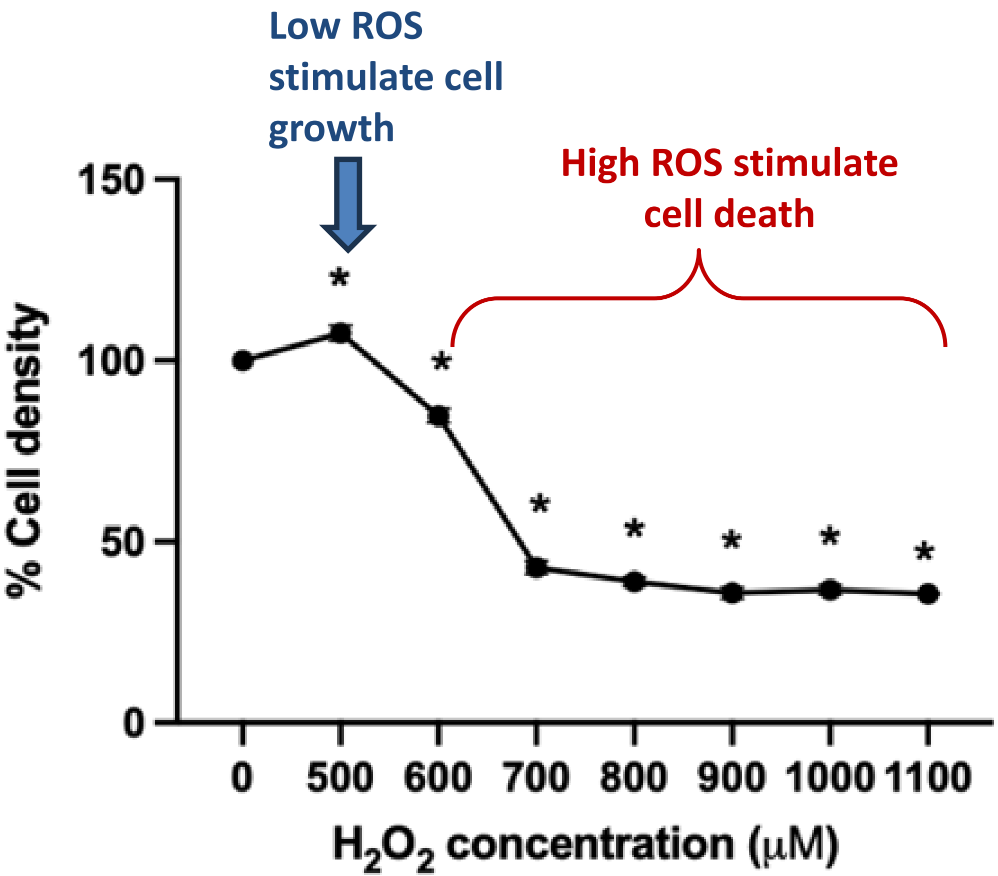
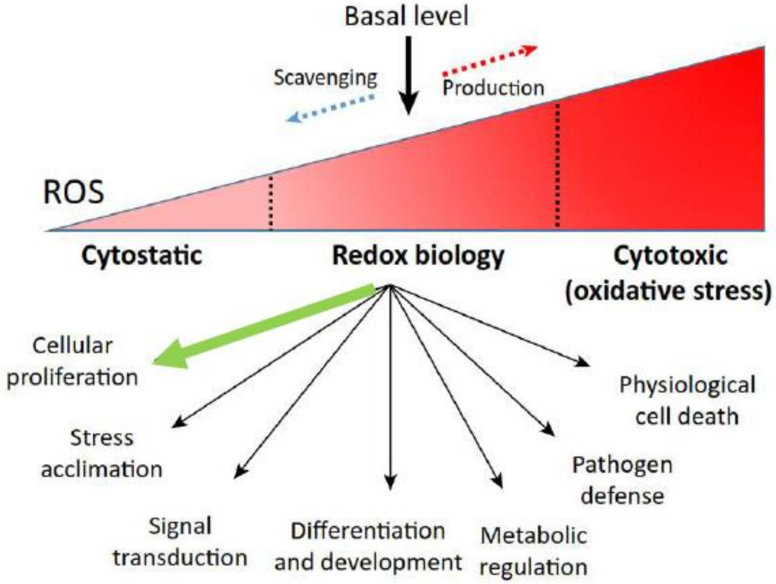
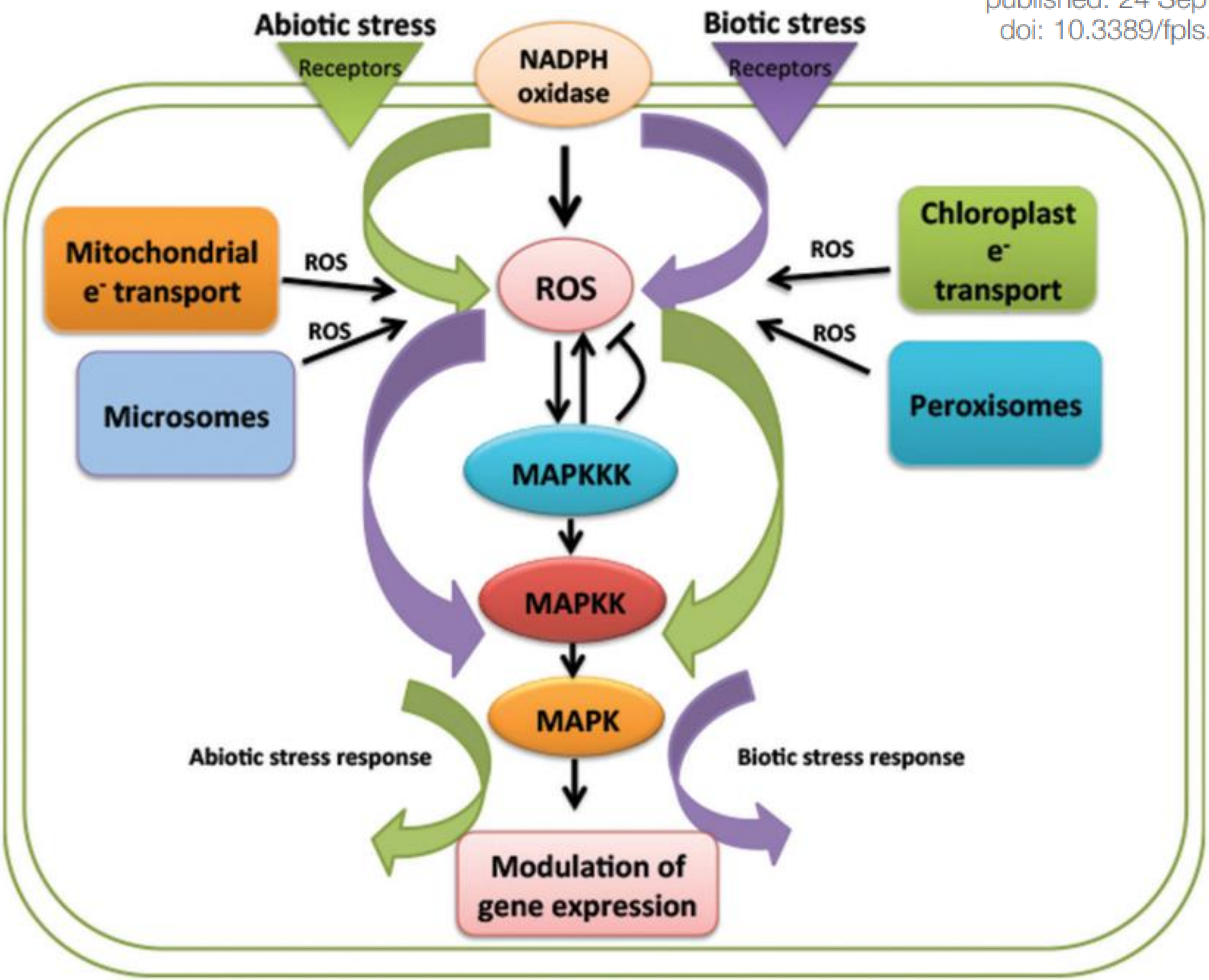
Oxidative stress adaptation



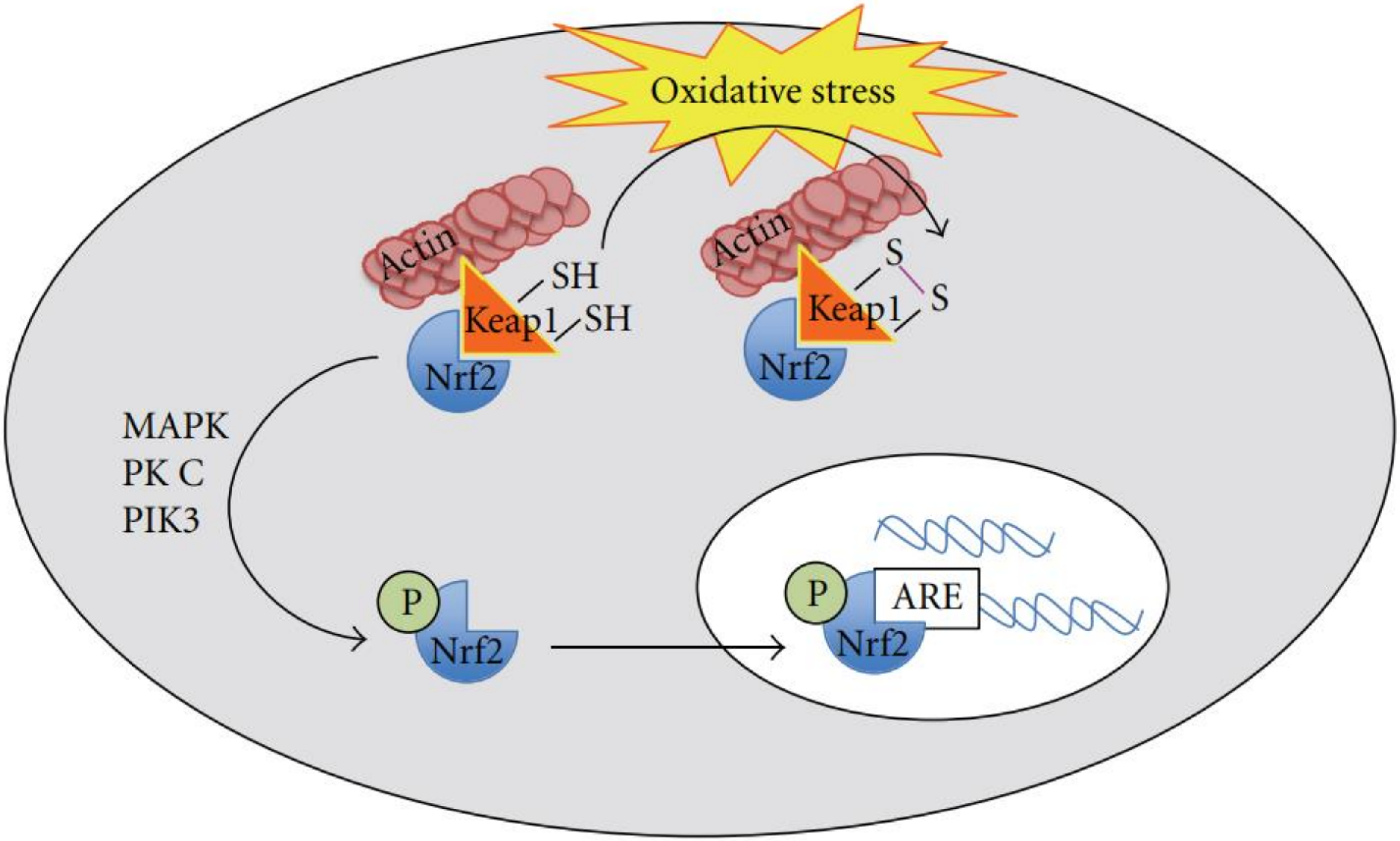


ROS regulation of mitogen activated protein kinases (MAPK) signaling pathway

REVIEW
published: 24 September 2015
doi: 10.3389/fpls.2015.00769



Oxidative stress induces Nrf2 dissociation from Keap1.



Hindawi Publishing Corporation
Journal of Toxicology
Volume 2011, Article ID 683728, 12 pages
doi:10.1155/2011/683728

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Effect of oxidative stress

Oxidative stress

↓

Over productions of ROS & RNS

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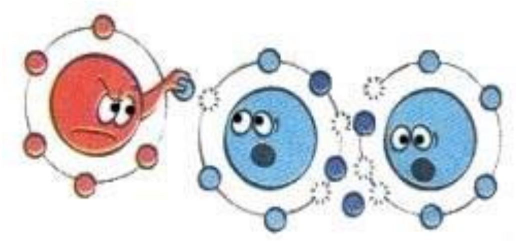
Oxidatively damage to biomolecules
- -Lipid
- -Protein
- -Nucleic acid

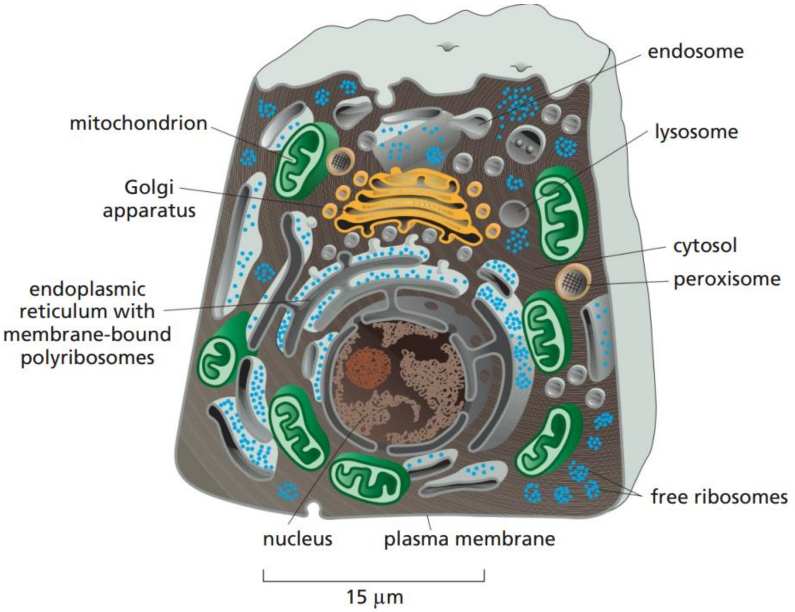
↓

Dysfunctions of biomolecules

↓

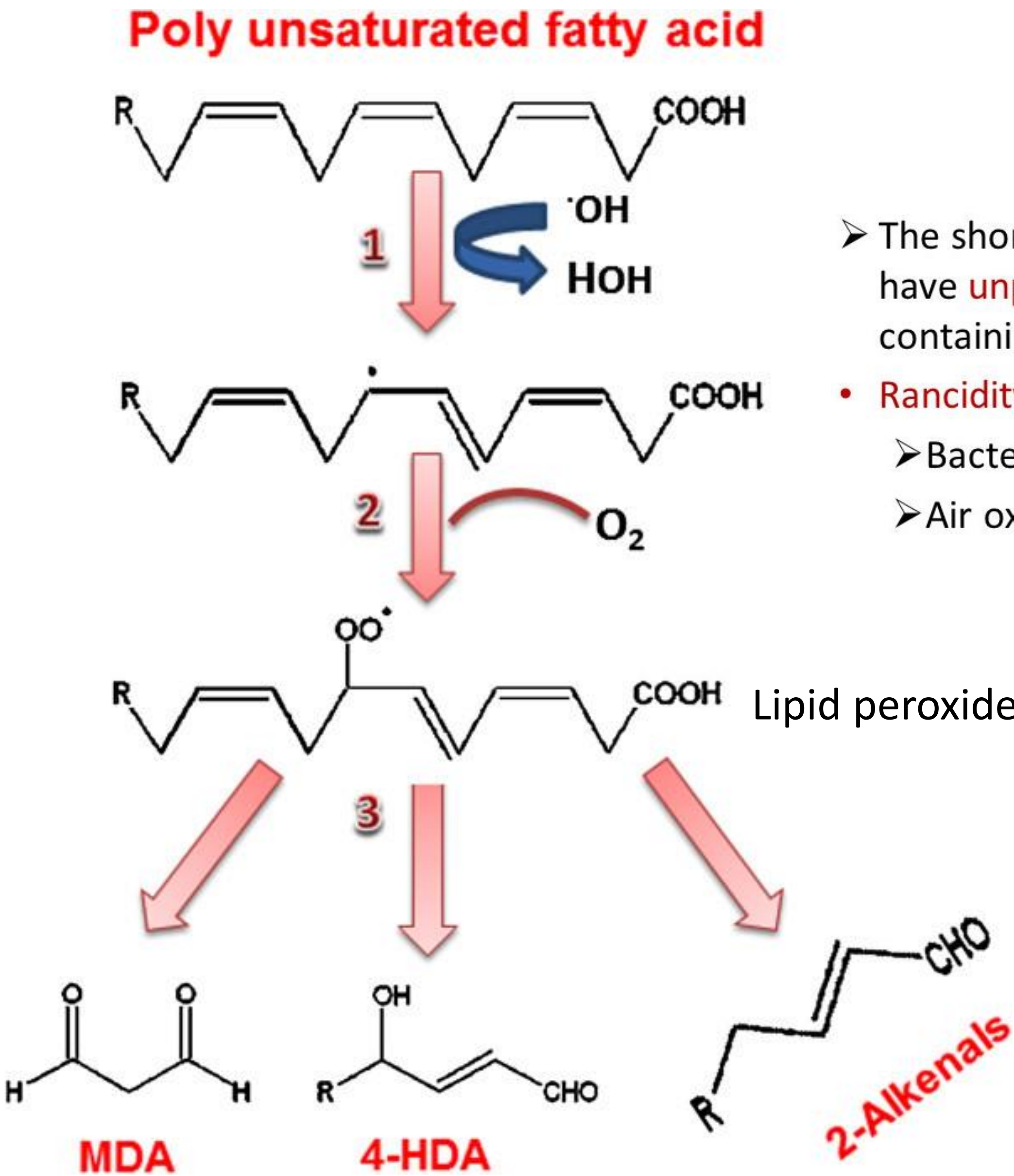
Oxidative stress-driven diseases





Oxidative damage to lipids

Oxidation

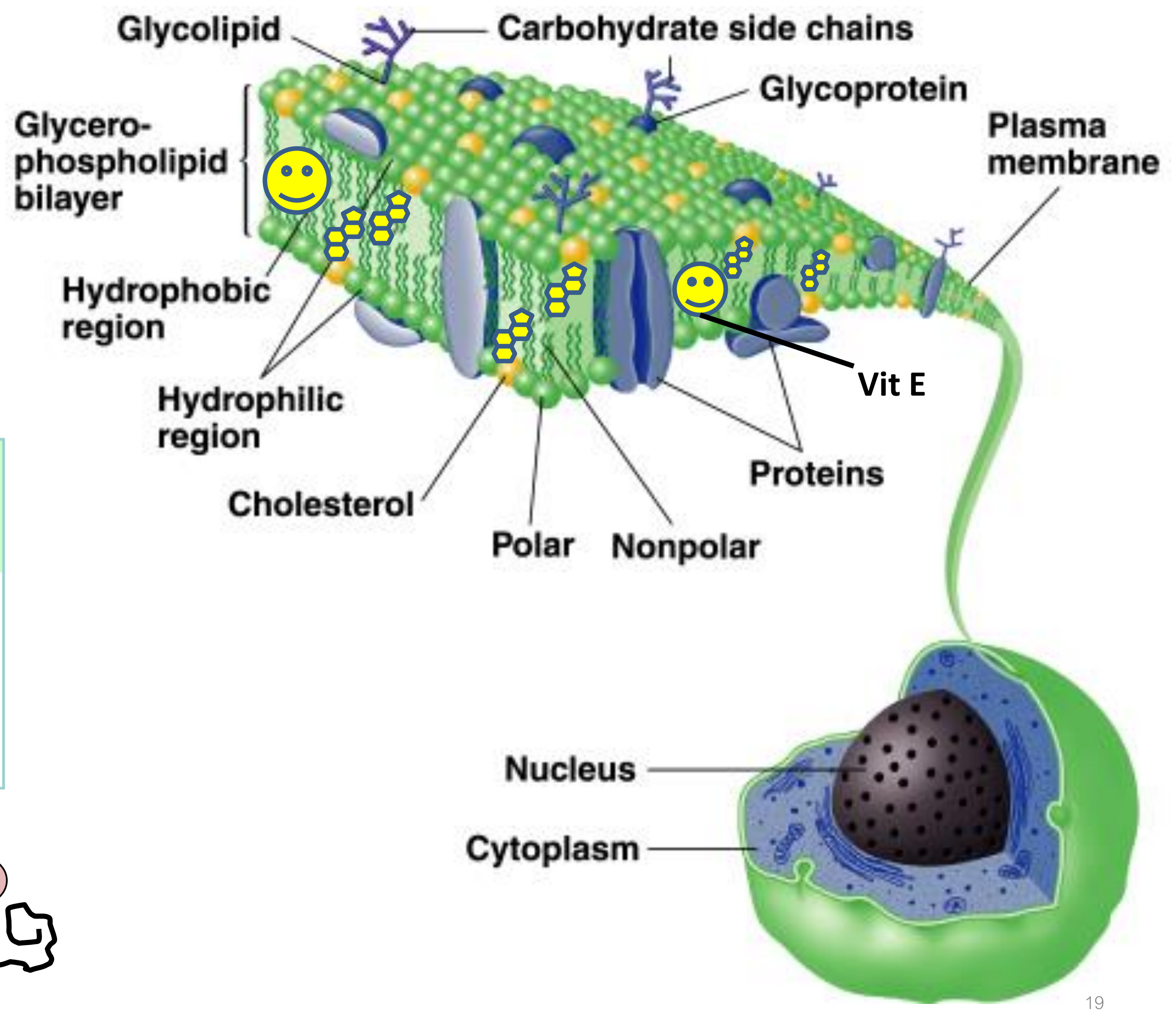


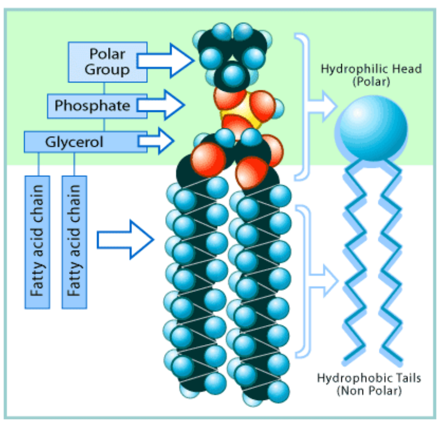
Lipid peroxide

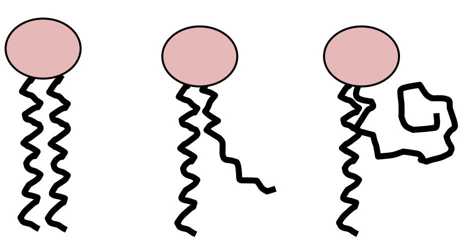
- The short-chain aldehydes and carboxylic acids often have unpleasant odors and flavors. Fats and oils containing them are said to have become *rancid*.
- Rancidity is due to a combination of two reactions:
  - Bacterial hydrolysis of ester bonds.
  - Air oxidation of alkene double bonds.

MDA = malondialdehyde, 4-HAD = 4-hydroxyalkenals

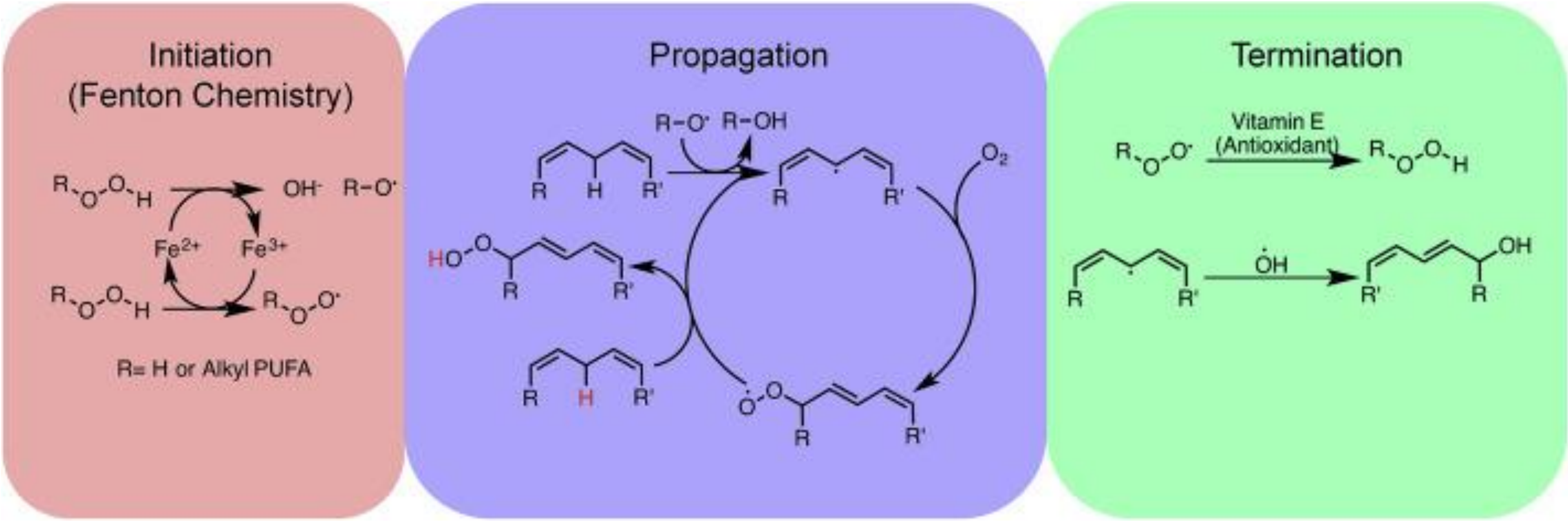
Biological membrane

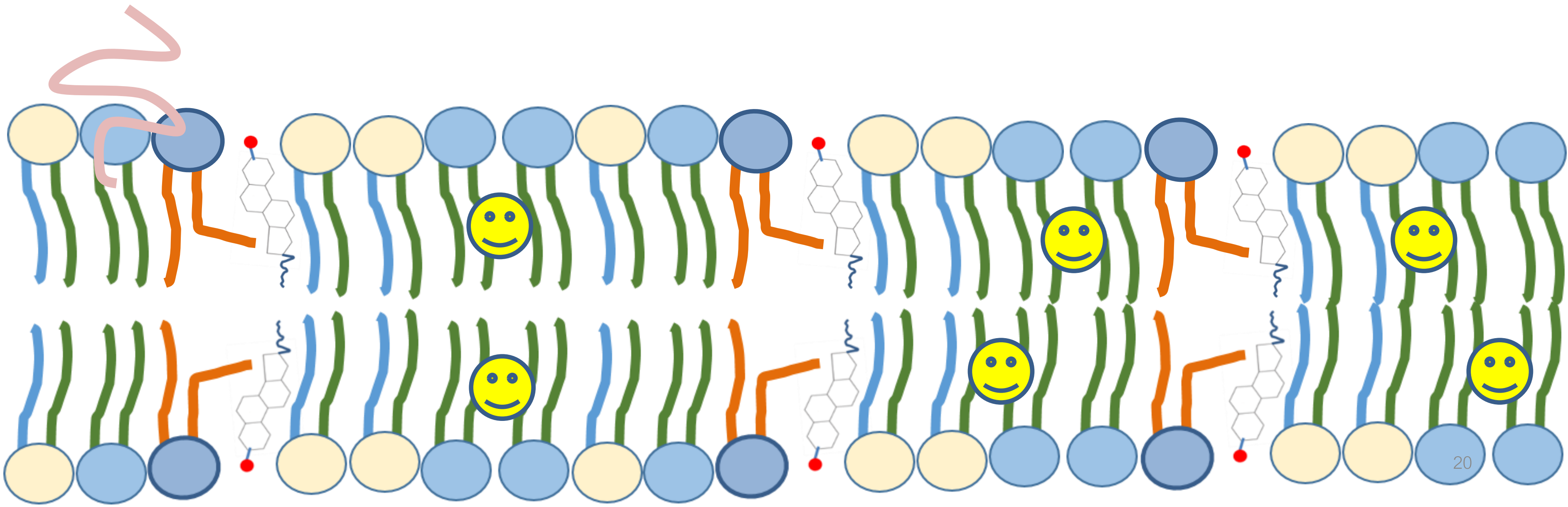


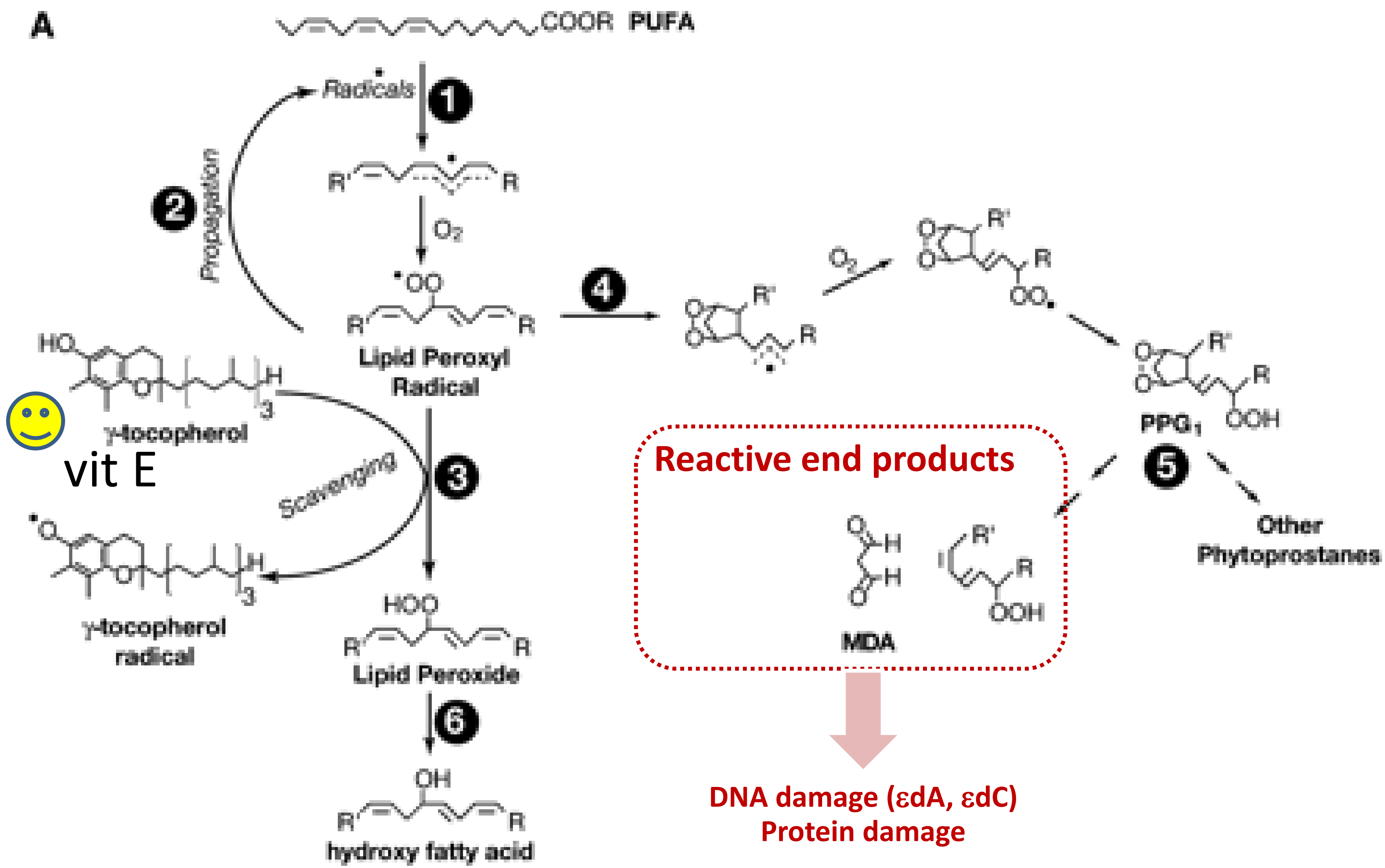




Lipid peroxidation

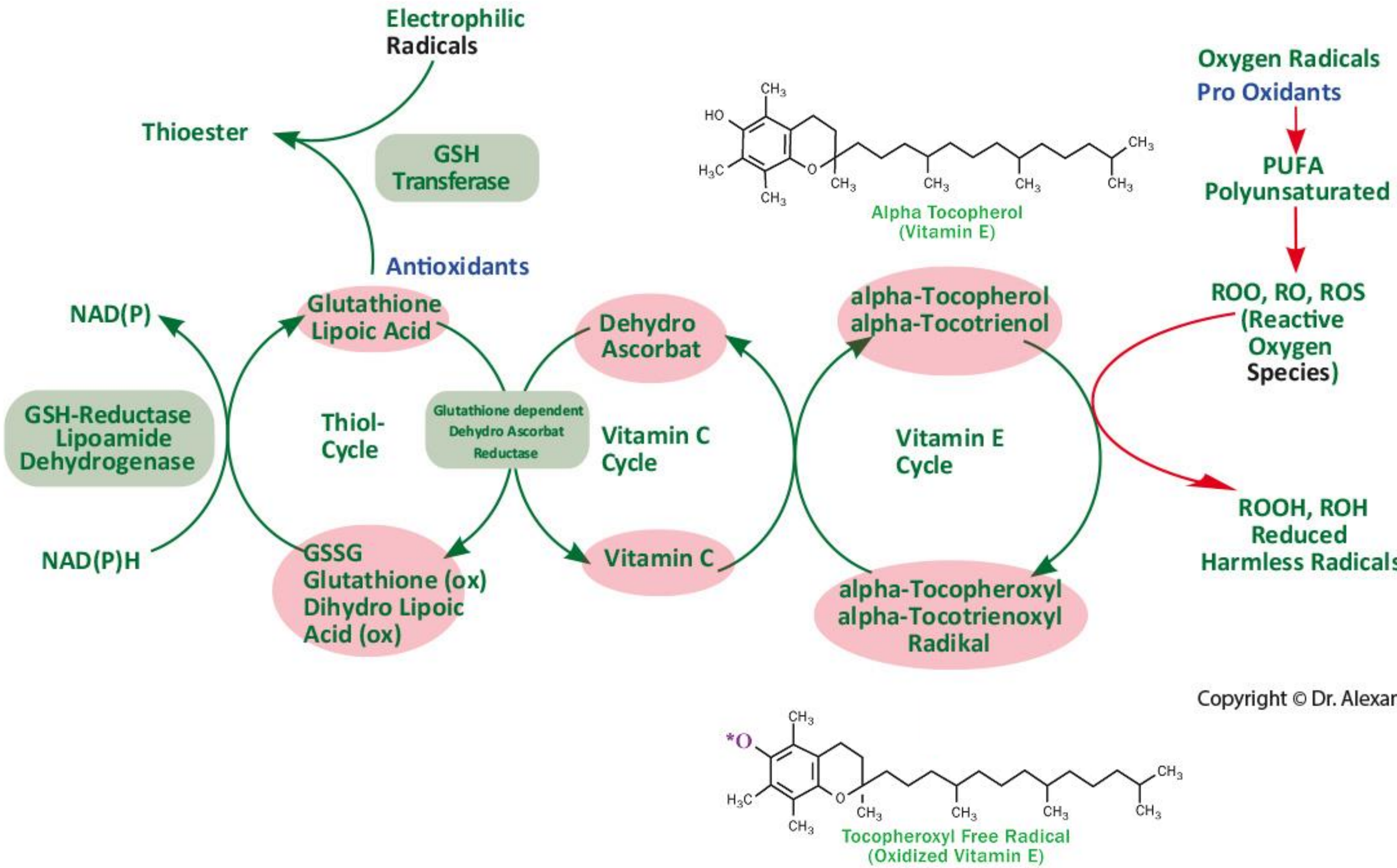






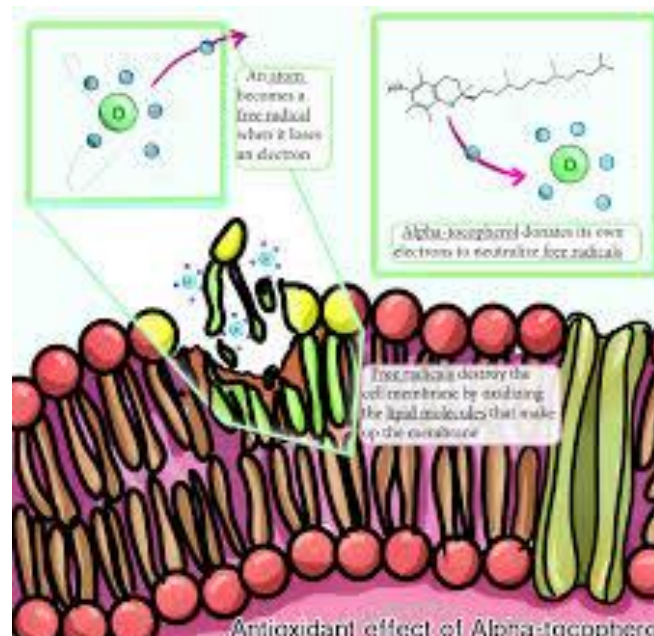
Chain breaking antioxidants

Antioxidative Network Vitamin E and Glutathione



Effect of lipid peroxidation

1. Covalent crosslinking; lipid-lipid, lipid-protein→ loss of fluidity
2. Membrane fluidity changes; more rigidity
3. Loss of membrane permeability
4. Increase iron permeability
5. Depletion of NADPH
6. Inactivation of membrane enzymes and receptors
7. DNA damage and mutation



Pansteatitis, or yellow fat disease

PANSTEATITIS OF UNKNOWN ETIOLOGY ASSOCIATED WITH LARGE-SCALE NILE CROCODILE (*CROCODYLUS NILOTICUS*) MORTALITY IN KRUGER NATIONAL PARK, SOUTH AFRICA: PATHOLOGIC FINDINGS

Author(s): Emily P. Lane, B.V.Sc., M. Phil., Dipl. A.C.V.P., Fritz W. Huchzermeyer, Dr. med. vet., Ph.D., Danny Govender, B.V.Sc., M.Sc., Roy G. Bengis, B.V.Sc. M.Sc., Ph.D., Peter E. Buss, B.V.Sc., M. med. vet., Markus Hofmeyr, B.V.Sc., Jan G. Myburgh, B.V.Sc., M. med. vet., Johan C. A. Steyl, B.V.Sc., M.Sc., Daniel J. PienaarB.Sc., Honours M.Sc. and Antoinette Kotze, B.Sc., Honours Ph.D.

Source: Journal of Zoo and Wildlife Medicine, 44(4):899-910.
Published By: American Association of Zoo Veterinarians
DOI: http://dx.doi.org/10.1638/2012-0264R.1
URL: http://www.bioone.org/doi/full/10.1638/2012-0264R.1

At least 216 crocodiles died during 2008-2012, especially in winter

Pathogenesis

-Steatitis (yellow fat disease), commonly results from an altered balance between oxidants and the levels of antioxidants causing lipid peroxidation

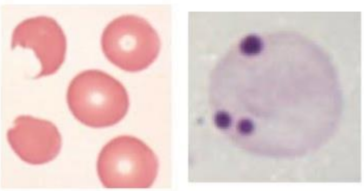
-The animals' inability to move

Possible causes:

-Vitamin E deficiency
-Microcystin poisoning
-Heavy metals and other pollutants
-Ingestion of affected animals
-Pathogens as yet unidentified

Glucose-6-Phosphate Dehydrogenase Deficiency

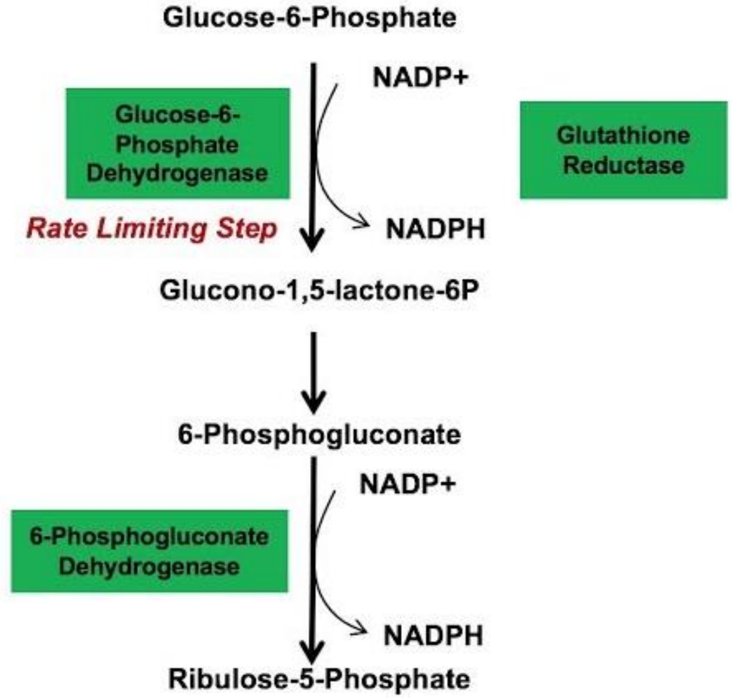
Hemolysis



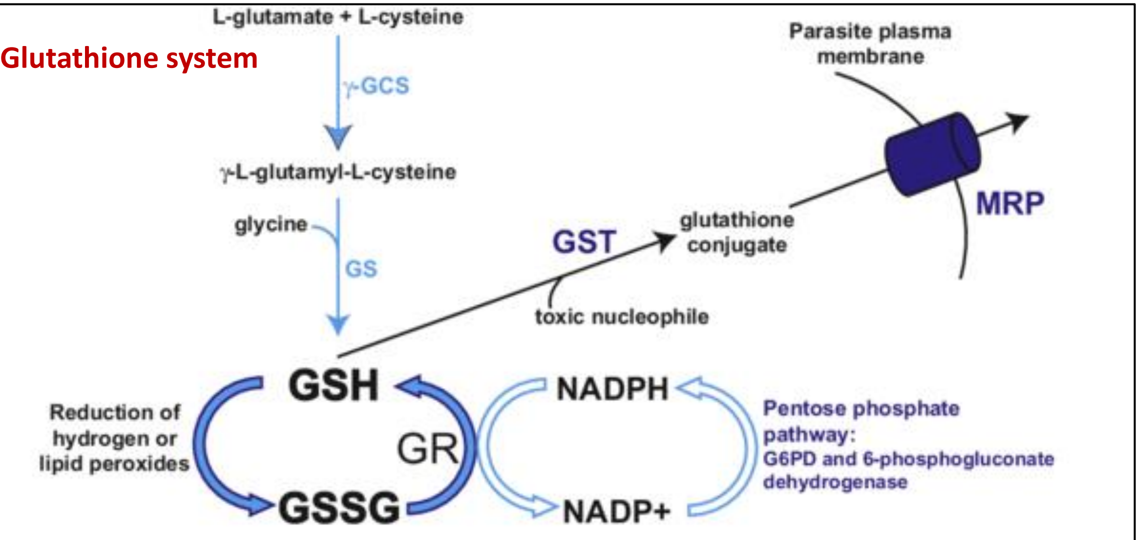
Broad bean

www.youtube.com

Pentose phosphate pathway (PPP)

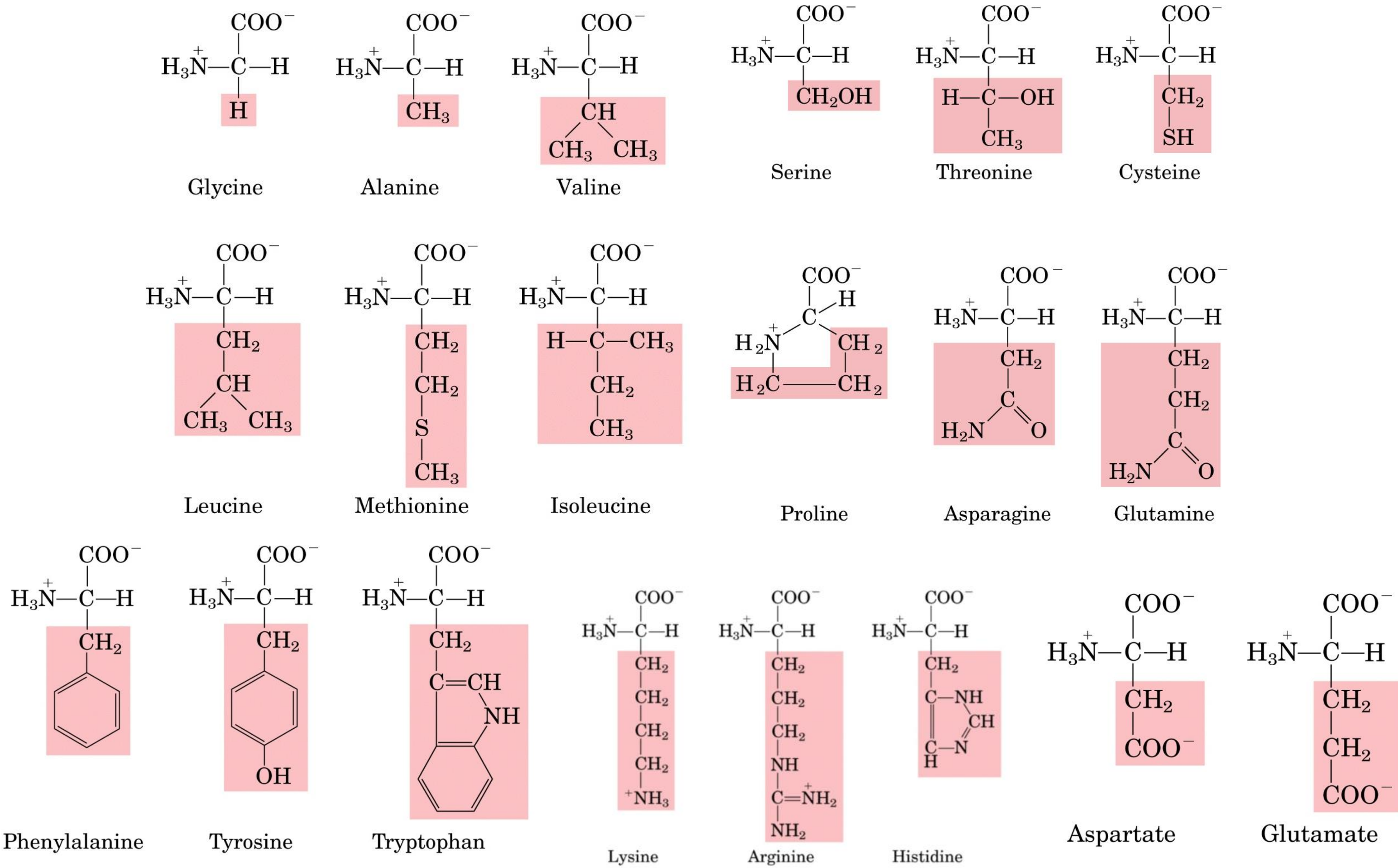


Glutathione system

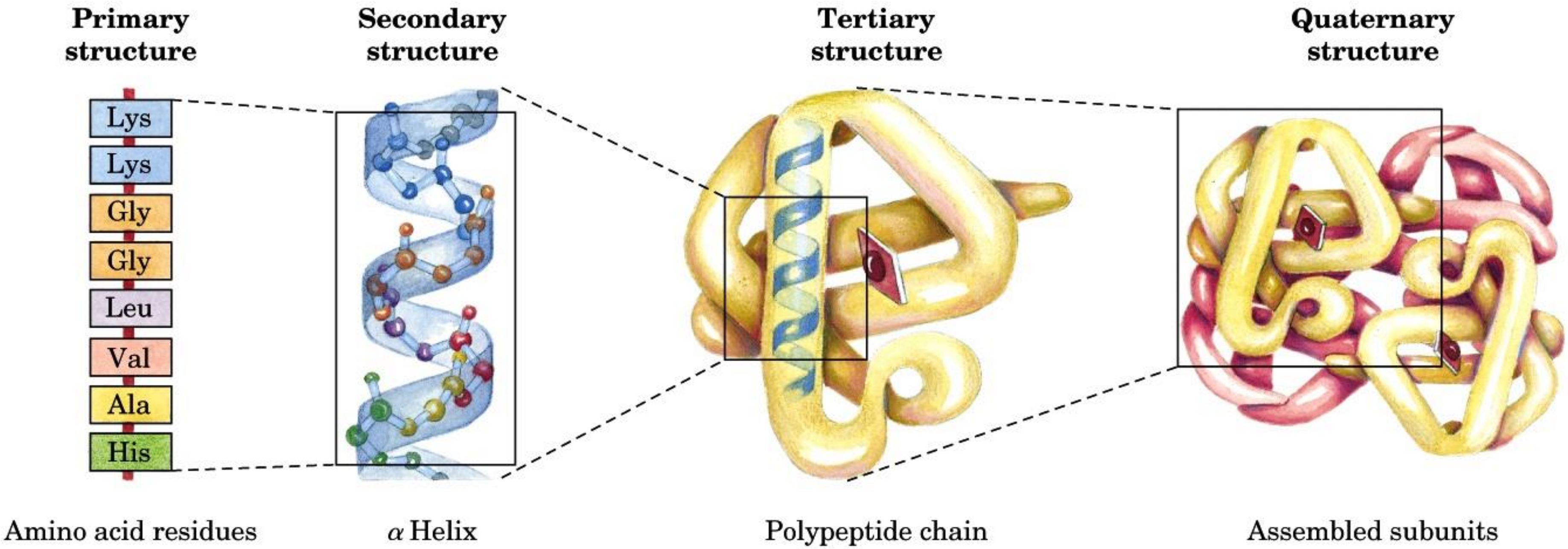


Oxidative damage to proteins

20 Amino acids: building block of proteins



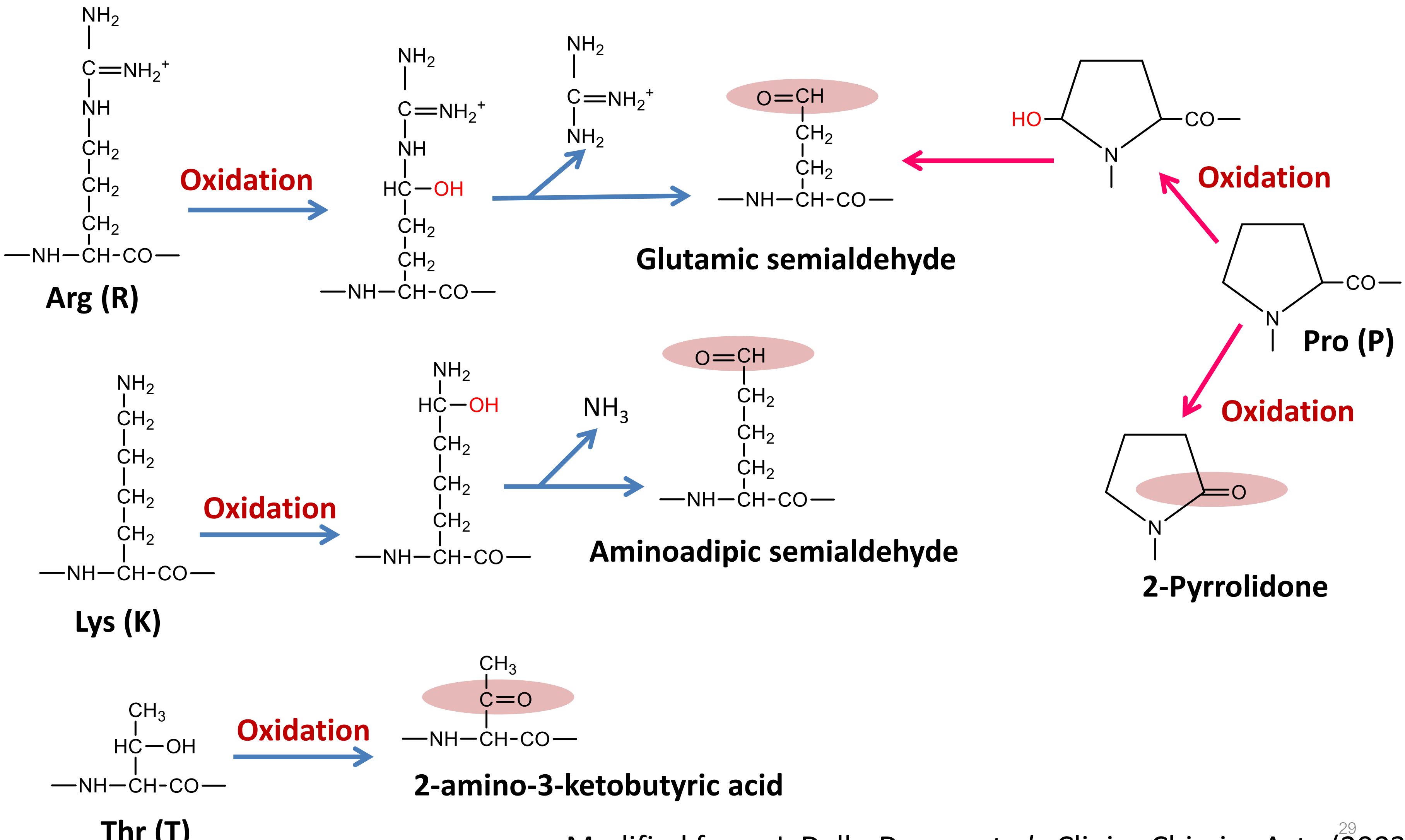
Protein structures: folding to function



“Right conformation=Native form=Function”

Protein carbonylation

Carbonylation is an irreversible and irreparable modification induced by metal-catalyzed oxidation {Amici, 1989 } that attacks the side chains of proline (P), arginine (R), lysine (K) and threonine (T) residues.



Modified from: I. Dalle-Donne *et al.* Clinica Chimica Acta (2003)

Table 1
Amino acid modifications by reactive oxygen and nitrogen species.

Amino acid	Modification by reactive oxygen and nitrogen species
Arginine	Glutamate semialdehyde
Proline	Glutamate semialdehyde 2-pyrrolidone
Lysine	2-Aminoadipate semialdehyde
Threonine	2-Amino-3-ketobutyric acid
Phenylalanine	Tyrosine (ortho, meta), nitrophenylalanine
Tyrosine	Dityrosine, 3,4-dihydroxyphenylalanine (DOPA), 3-chlorotyrosine, 3-bromotyrosine, 3,5-dibromotyrosine, 3,5-dichlorotyrosine, 3-nitrotyrosine
Tryptophan	Kynurenine, *N*-formylkynurenine, 5-hydroxytryptophan, 7-hydroxytryptophan, hydroxyperoxides, 6-nitrotryptophan
Histidine	2-Oxohistidine, aspartate, asparagine
Cysteine	Disulfid(-*S*-*S*-)protein bonds, thiyl radicals
Methionine	Methionine sulfoxide, methionine sulfone
Leucine	Hydroxyleucine
Glycine	Aminomalonic acid
Valine	Valine hydroperoxides

Chondrogianni et al, 2014

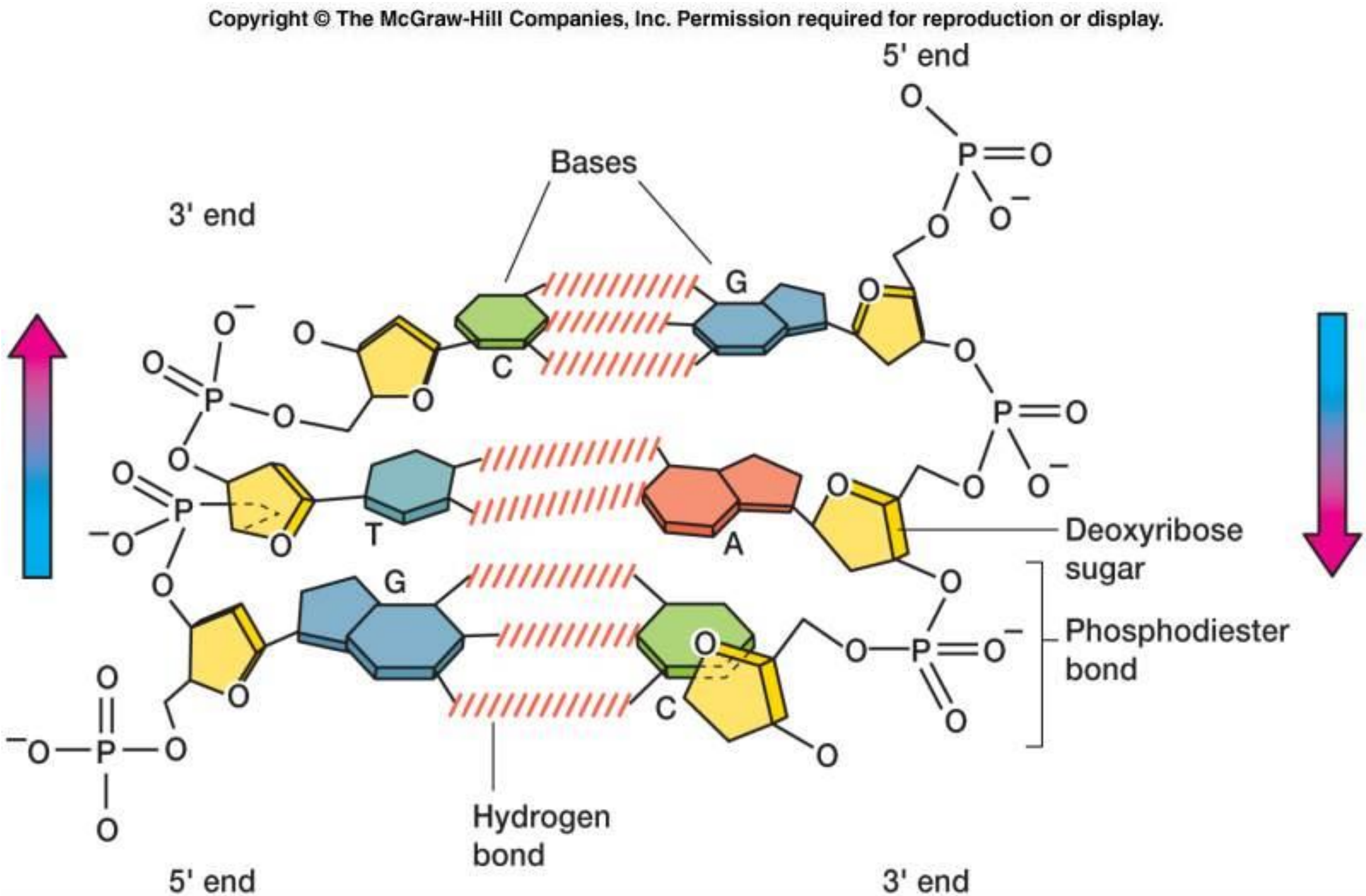
Effect of oxidative stress on proteins

1. Fragmentation of proteins
2. Formation of new reactive species
3. Dimerization or aggregation; DNA-Protein crosslinking
4. Unfolding or conformational changes => activity change
5. Loss of structural or functional activity
6. Alterations in cellular handling/turnover
7. Modulation of cell signalling; effects on gene regulation & expression
8. Induction of apoptosis and necrosis

Protein conformational change and dysfunction

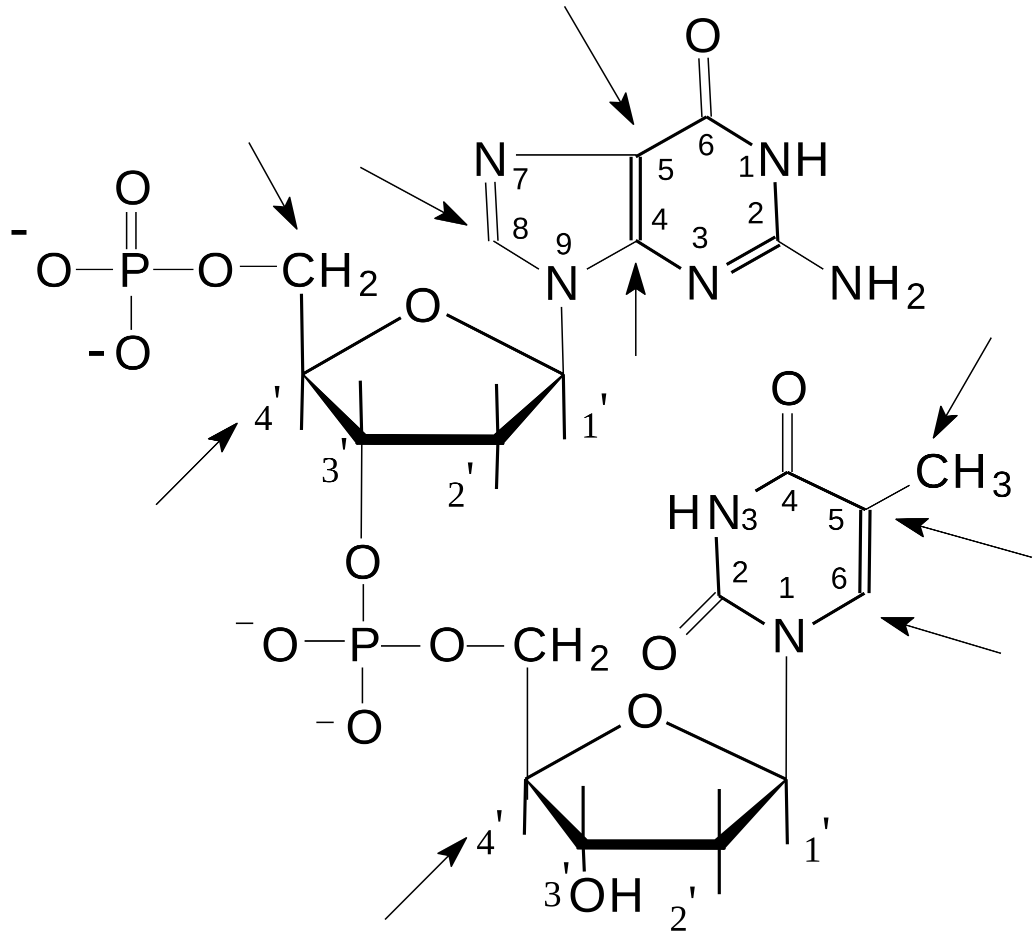
Oxidative damage to DNA

DNA structure



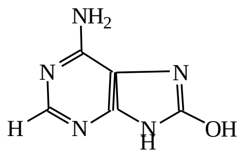
https://global.britannica.com/science/DNA

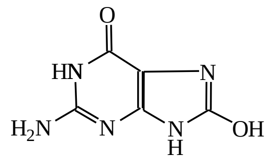
Hot Spots for Free Radical Attack

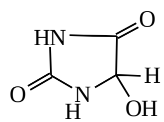


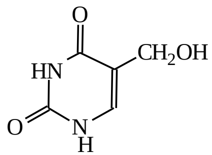
Examples of Oxidized DNA Bases (DNA adducts)

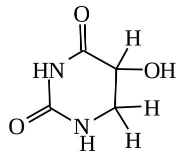
Adapted from: Dizdaroglu M. (1992) *Free Radic Biol Med.* 10:225-242. Dizdaroglu M. (2002) *Free Radic Biol Med.* 32:1102-1115.

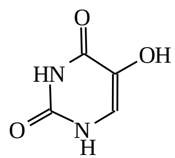

8-hydroxyadenine

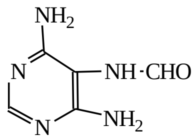

8-hydroxyguanine

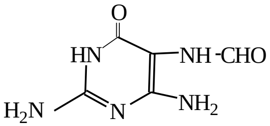

5-hydroxy hydantoin

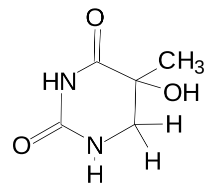

5-hydroxymethyluracil

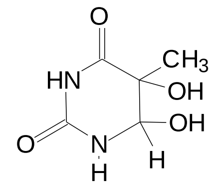

5-hydroxy-6-hydrouracil

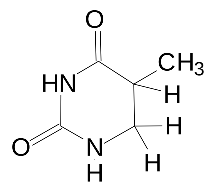

5-hydroxyuracil

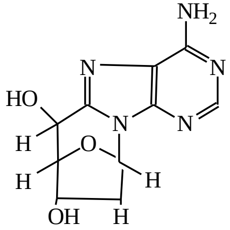

4,6-Diamino-5-formamidopyrimidine

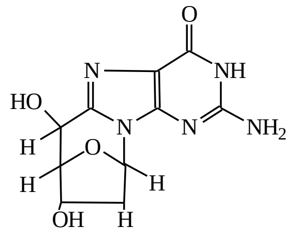

2,6-Diamino-4-hydroxy-formamidopyrimidine

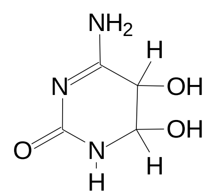

5-hydroxy-6-hydrothymine

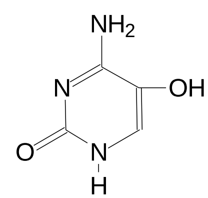

Thymine glycol (cis and trans)

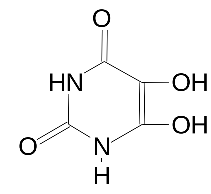

5,6-dihydrothymine

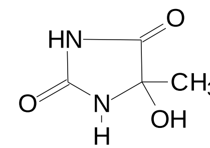

8,5'-cyclo-2'-deoxyadenosine


8,5'-cyclo-2'-deoxyguanosine


Cytosine glycol


5-hydroxycytosine


5,6-dihydroxy uracil


5-hydroxy-5-methylhydantoin

Effect of oxidative DNA damage

1. Mutation
2. DNA breaks
3. Inductions of DNA damage response proteins
   - DNA repair
   - Cell cycle arrest
   - Senescence
   - Apoptosis
4. Activation of DNA repairing system
5. NAD^+ depletion ➡ Inhibition of longevity gene (SIRT)
6. Epigenetic changes

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    - 5.4 Repair
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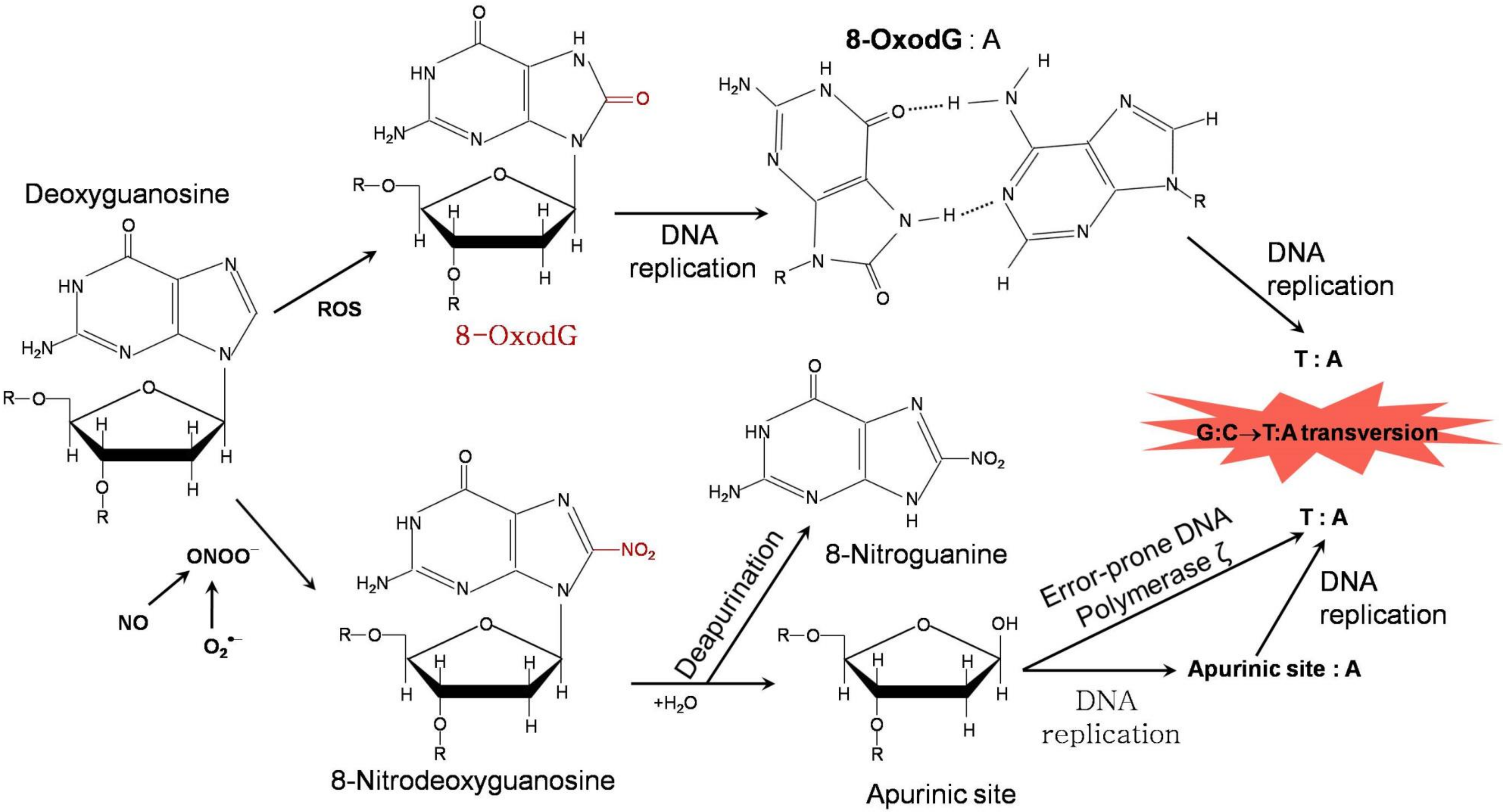
    - 5.6 Death
6. Oxidative stress-related diseases

Oxidative DNA damage induces point mutation

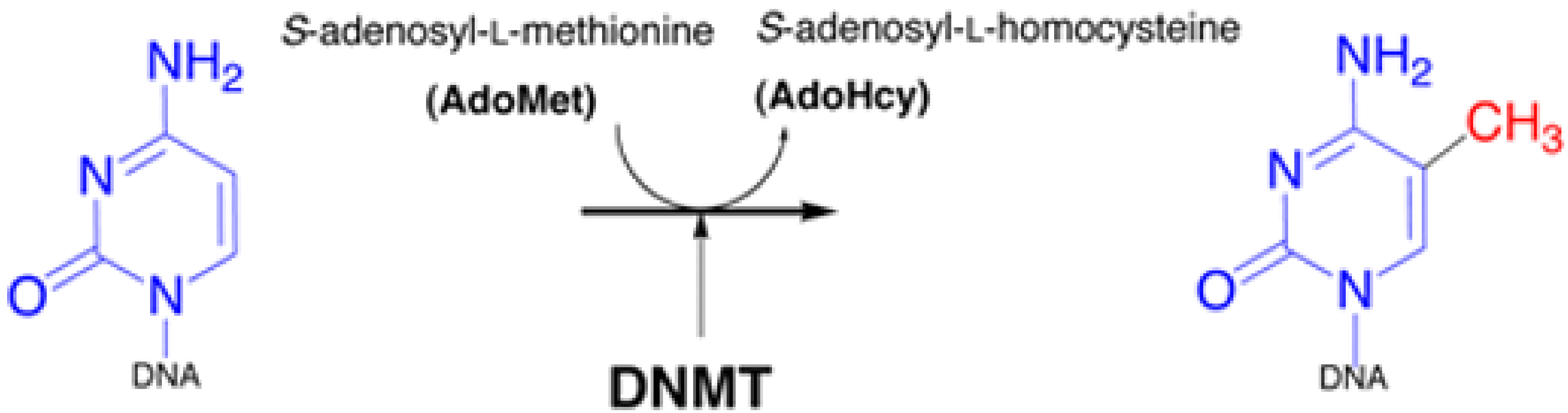


Murata et al., 2012

Oxidative stress induce epigenetic changes

DNA methylation

(SAM)



DNMT

(DNA methytransferase)

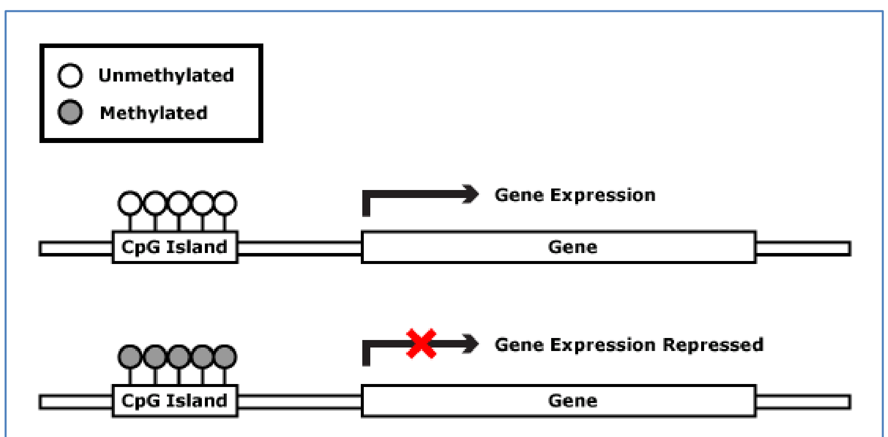
cytosine

C

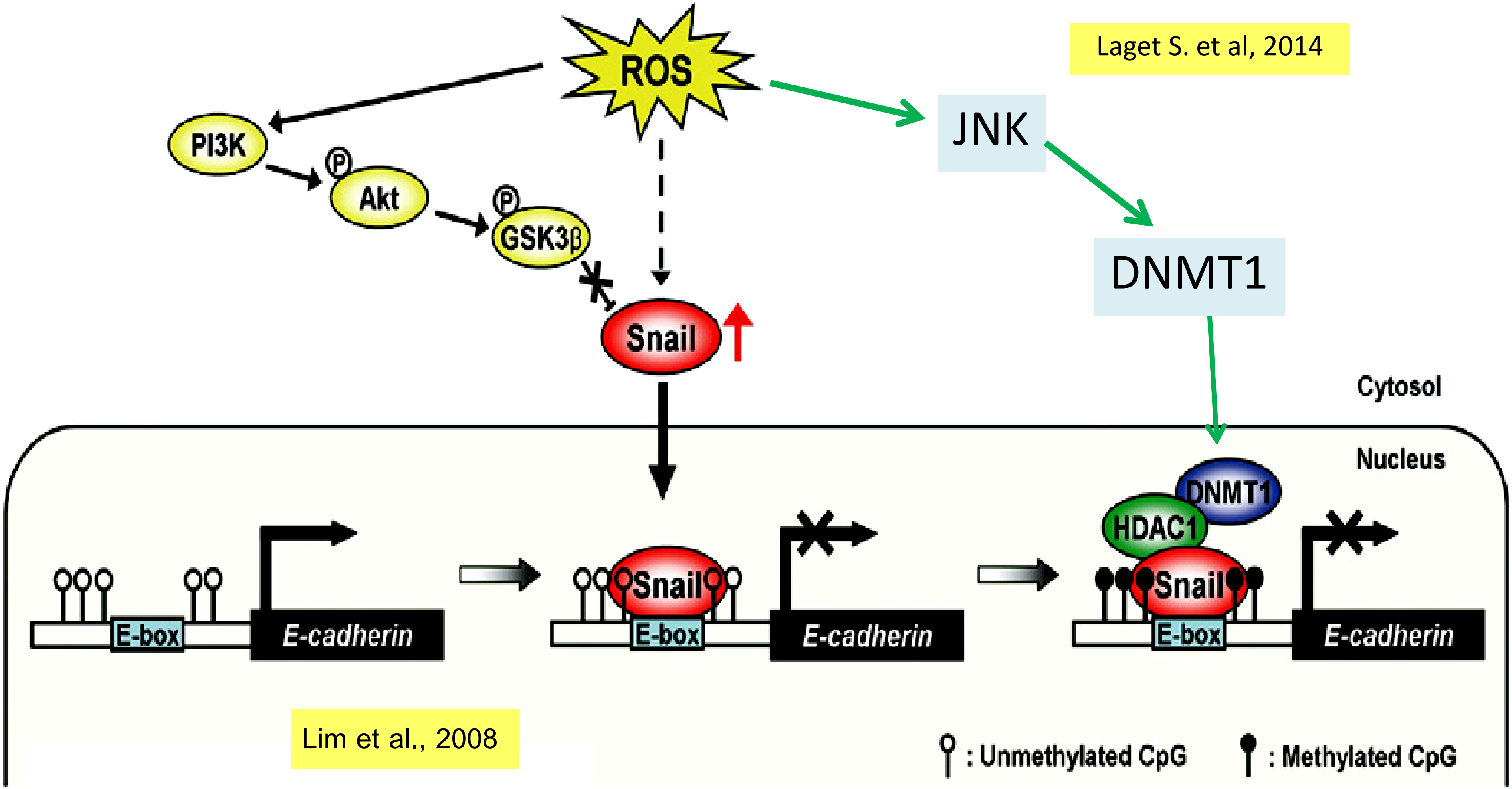
5-methylcytosine

^{Me}C

@ CpG site → **High frequency of CpG sites** → **CpG island**

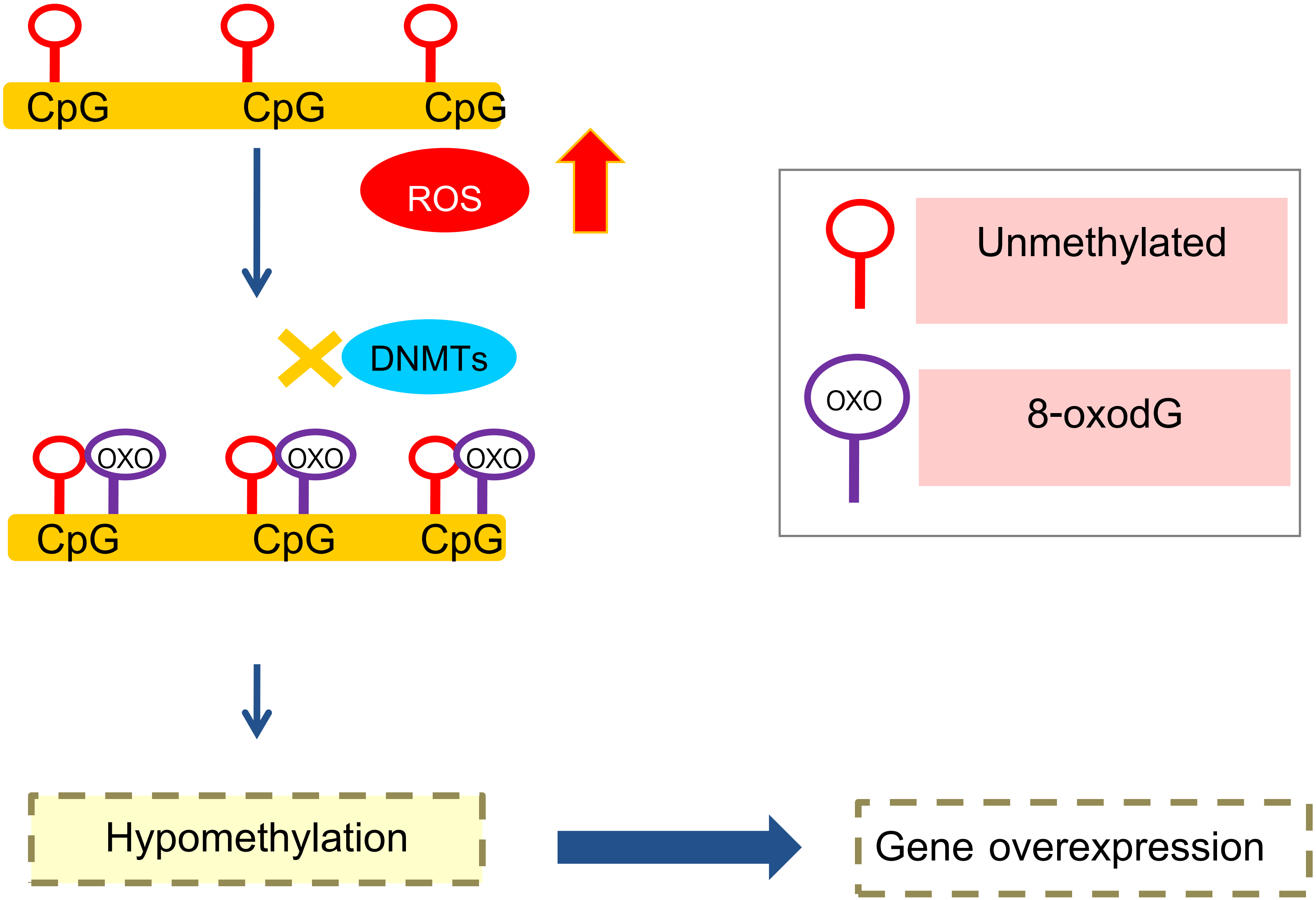


ROS-induced DNA hypermethylation



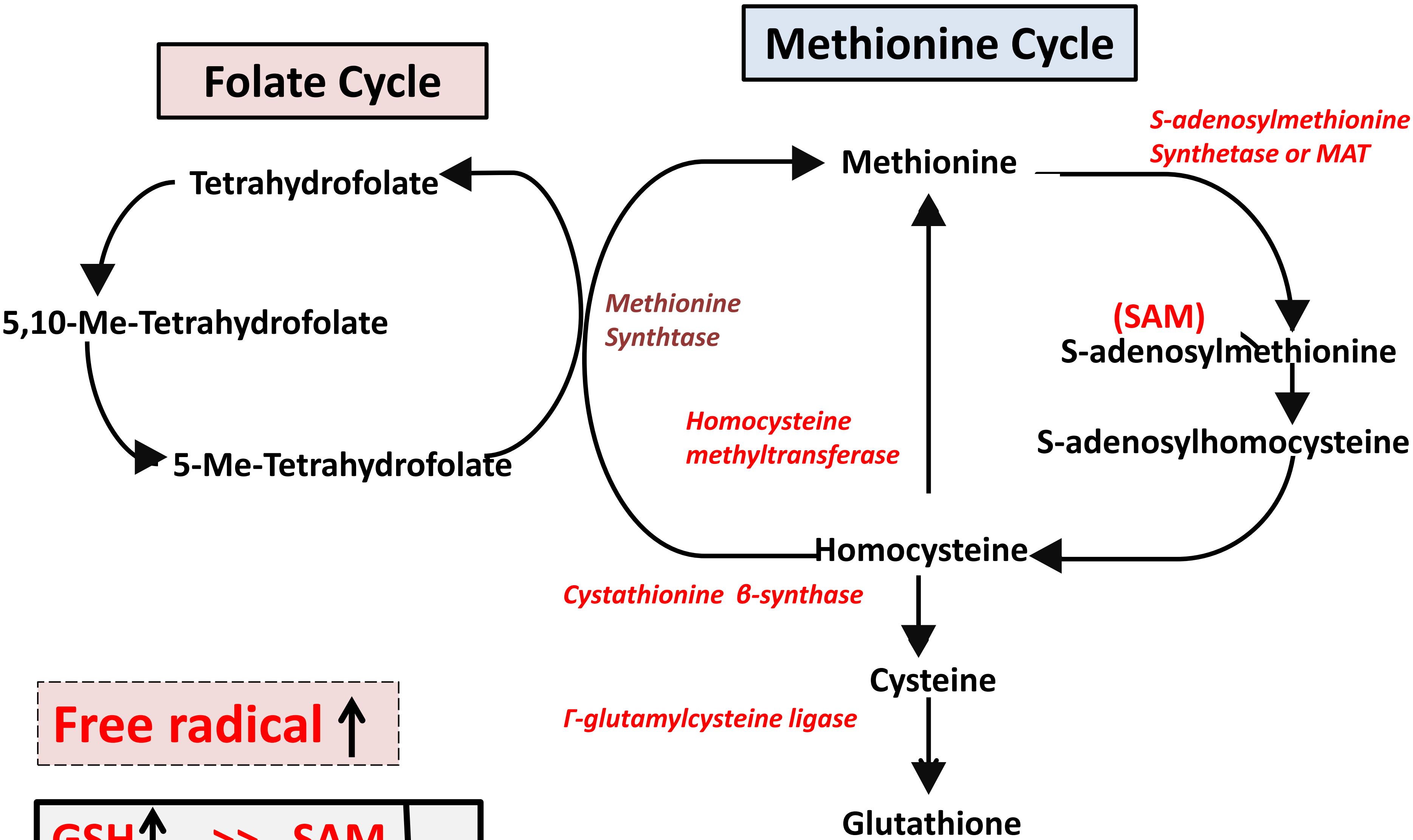
DNMT1= DNA methyltransferase 1

ROS-induced DNA hypomethylation



Donkena et al., 2010

ROS-induced DNA hypomethylation



Free radical ↑

GSH ↑ >> SAM ↓

Hitchler M. et al. Free Radical Biology and Medicine, 2007

Summary: Oxidative damage and epigenetic changes

Oxidative stress

Hypermethylation

- Induction of DNMT1 expression & its activity

Hypomethylation

- DNA damage formation
- Generation of GSH

Outline

1. Definitions of oxidants and antioxidants
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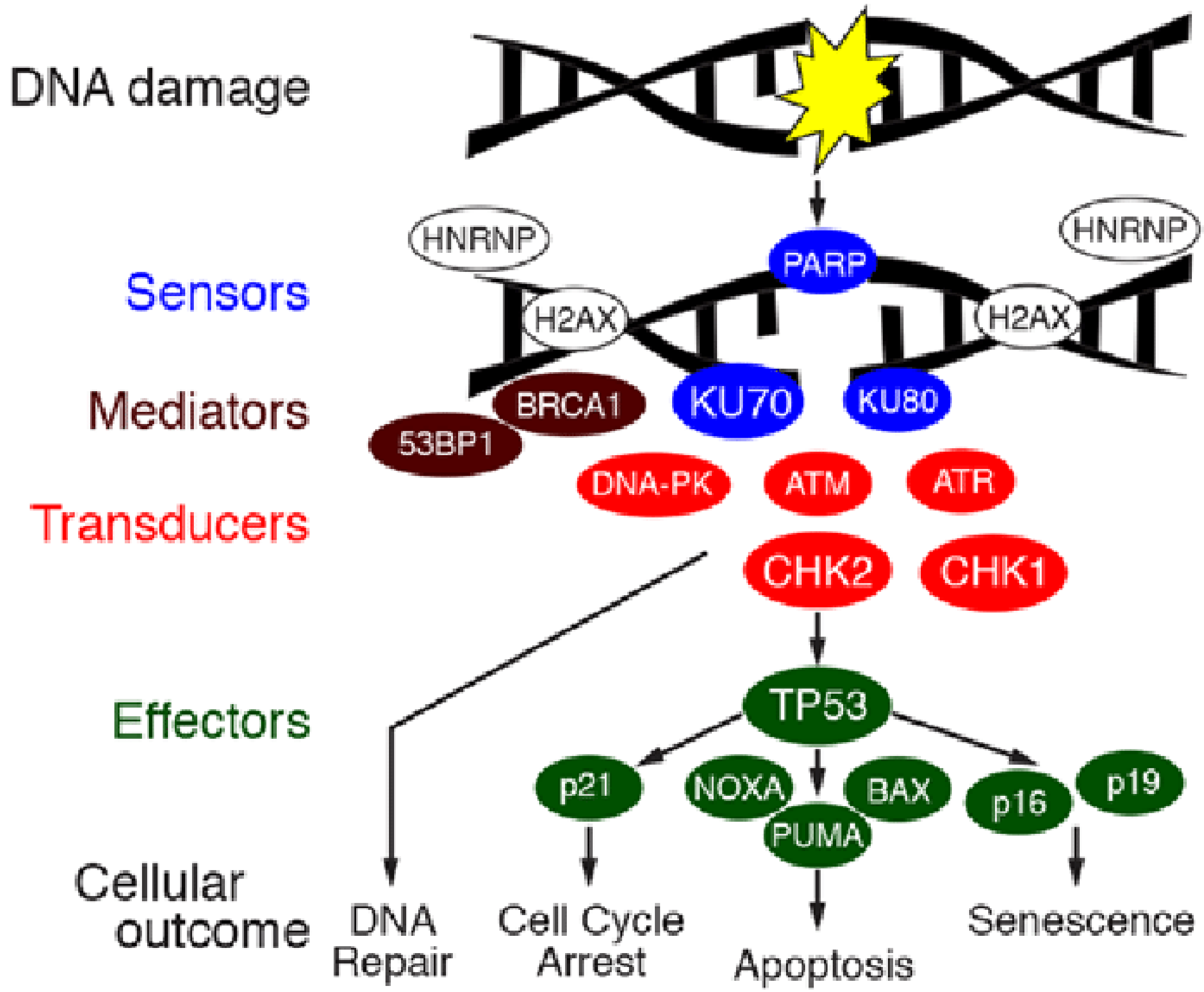
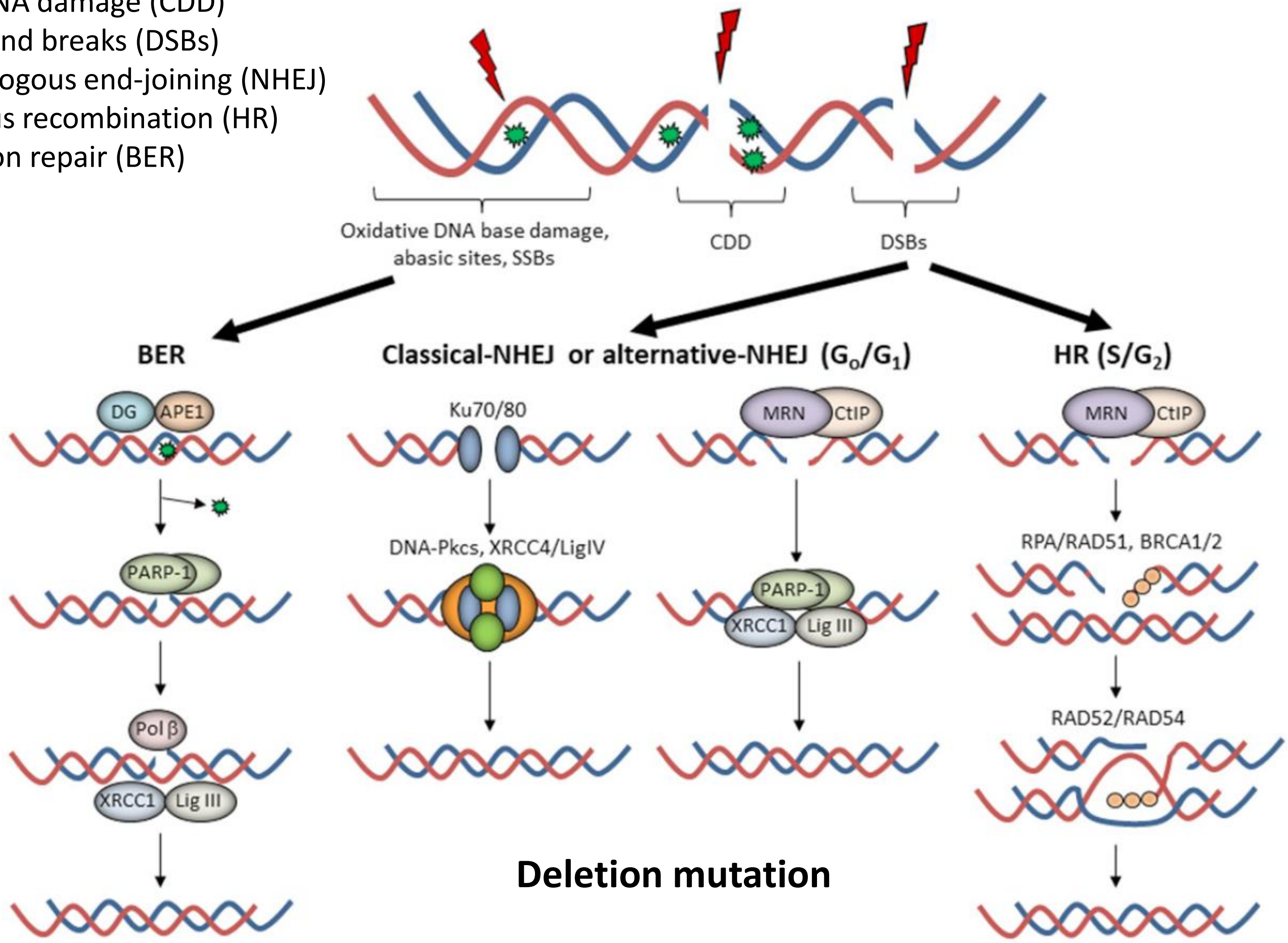
DNA damage response proteins



Oxidative DNA damage induces SSBs, CDD, DSBs and DNA repairing system

Single-strand breaks (SSBs)
Complex DNA damage (CDD)
Double strand breaks (DSBs)
Non-homologous end-joining (NHEJ)
Homologous recombination (HR)
Base excision repair (BER)



Deletion mutation

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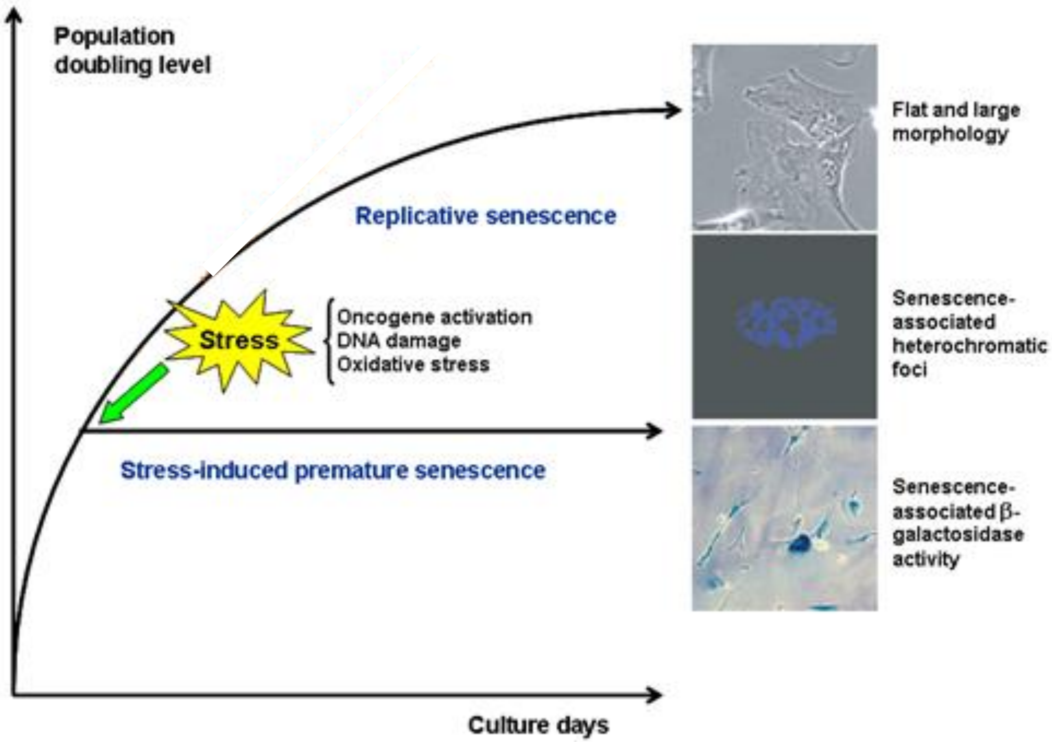
Cellular senescence

Senescence cells are irreversibly arrested in the G1 phase of the cell cycle and are no longer able to divide despite remaining viable and metabolically active for long periods of time.

Two types of cellular senescence

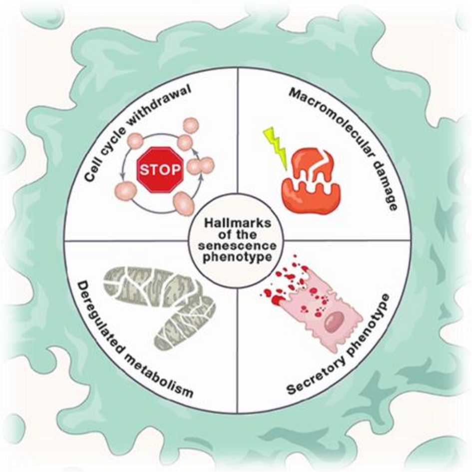
-Replicative senescence; RS

-Stress-induced premature senescence; SIPS



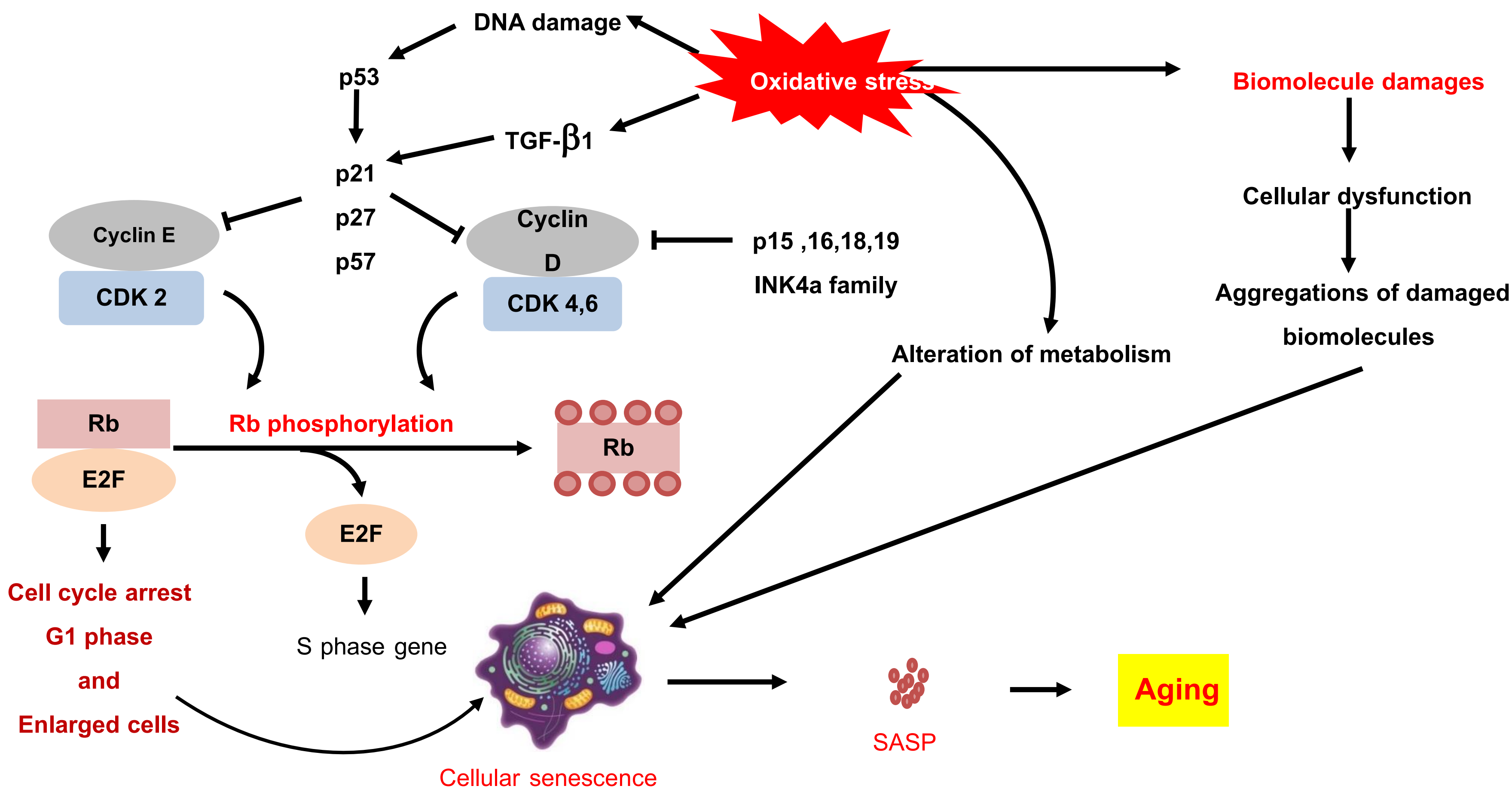
Cellular senescence phenotypes

G1 cell cycle arrest
Damage of biomolecules
Enlarged cell size
Increased SASP
Senescence-associated–galactosidase activity (SA β-gal)
Increased metalloproteinase activity
Alterations of anti-aging (longevity) and aging gene expressions
Decreased induction of heat shock proteins
Alteration of metabolism

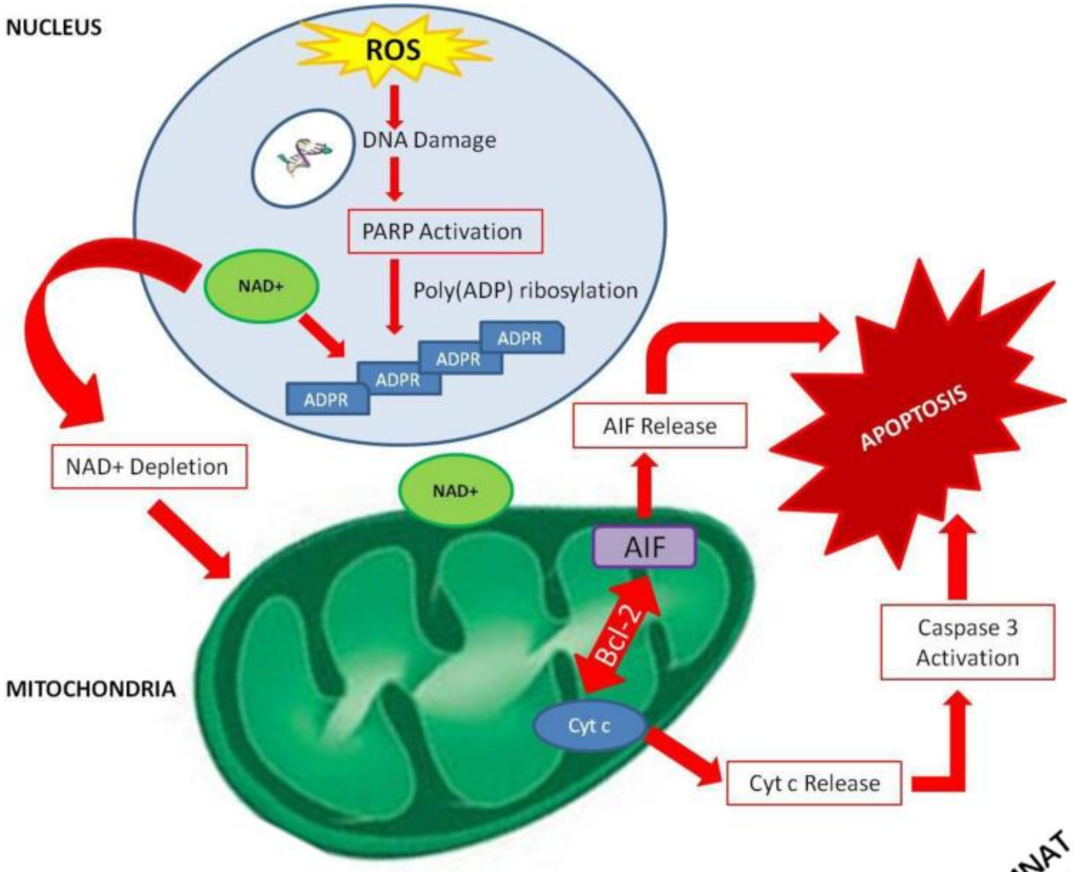


Toussaint O, *et.al*. IJBCB. 2002

Oxidative stress-induced cellular senescence



DNA damage decreases NAD$^+$

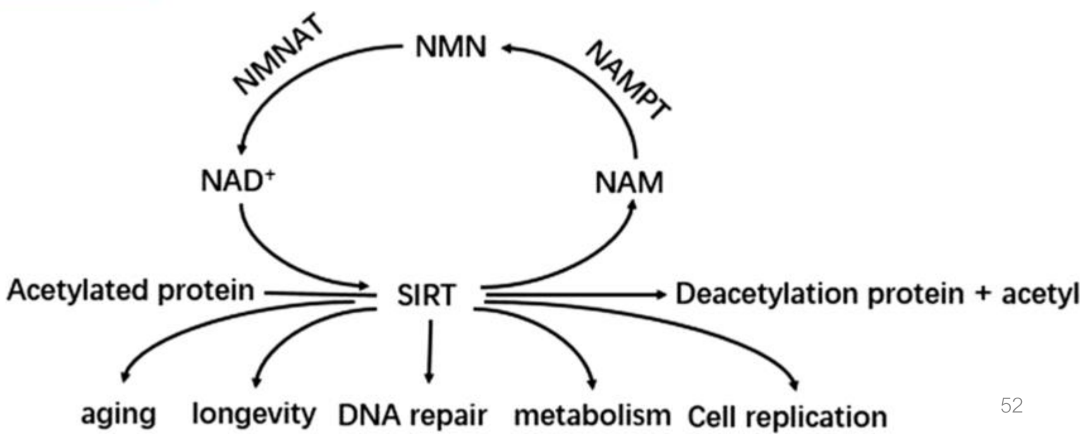


Massudi H. *et.al.,* Redox Rep. 2012

Decrease longevity activity

↓

Aging



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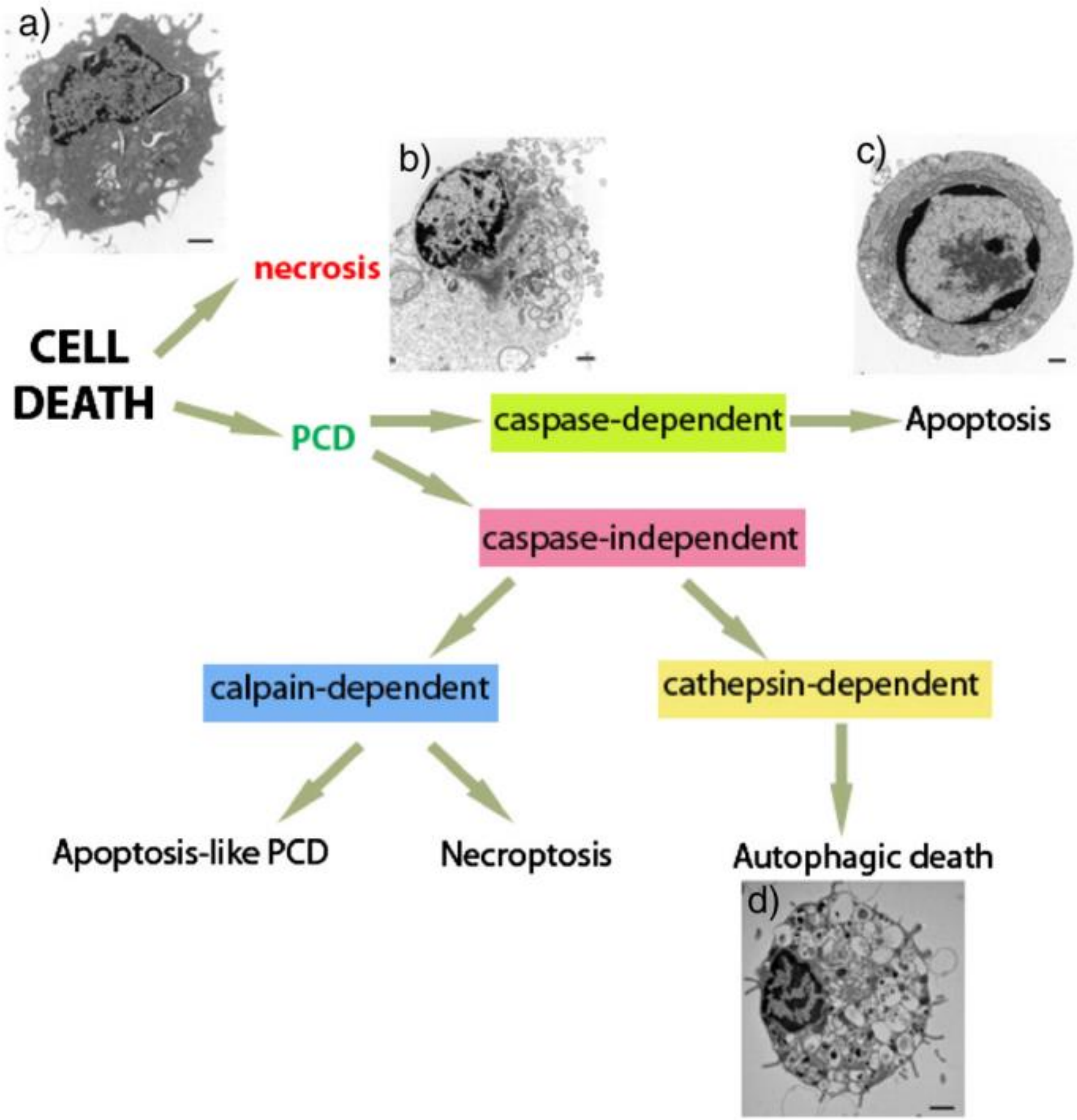
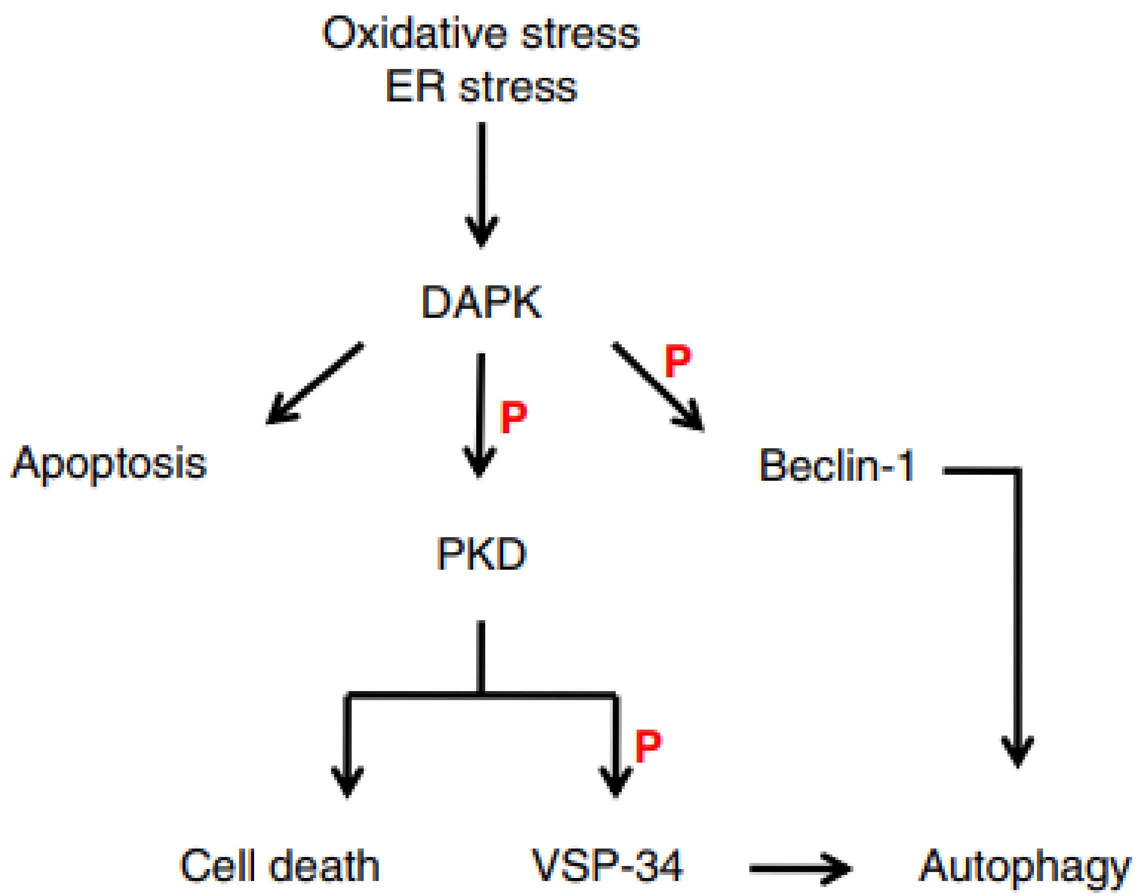


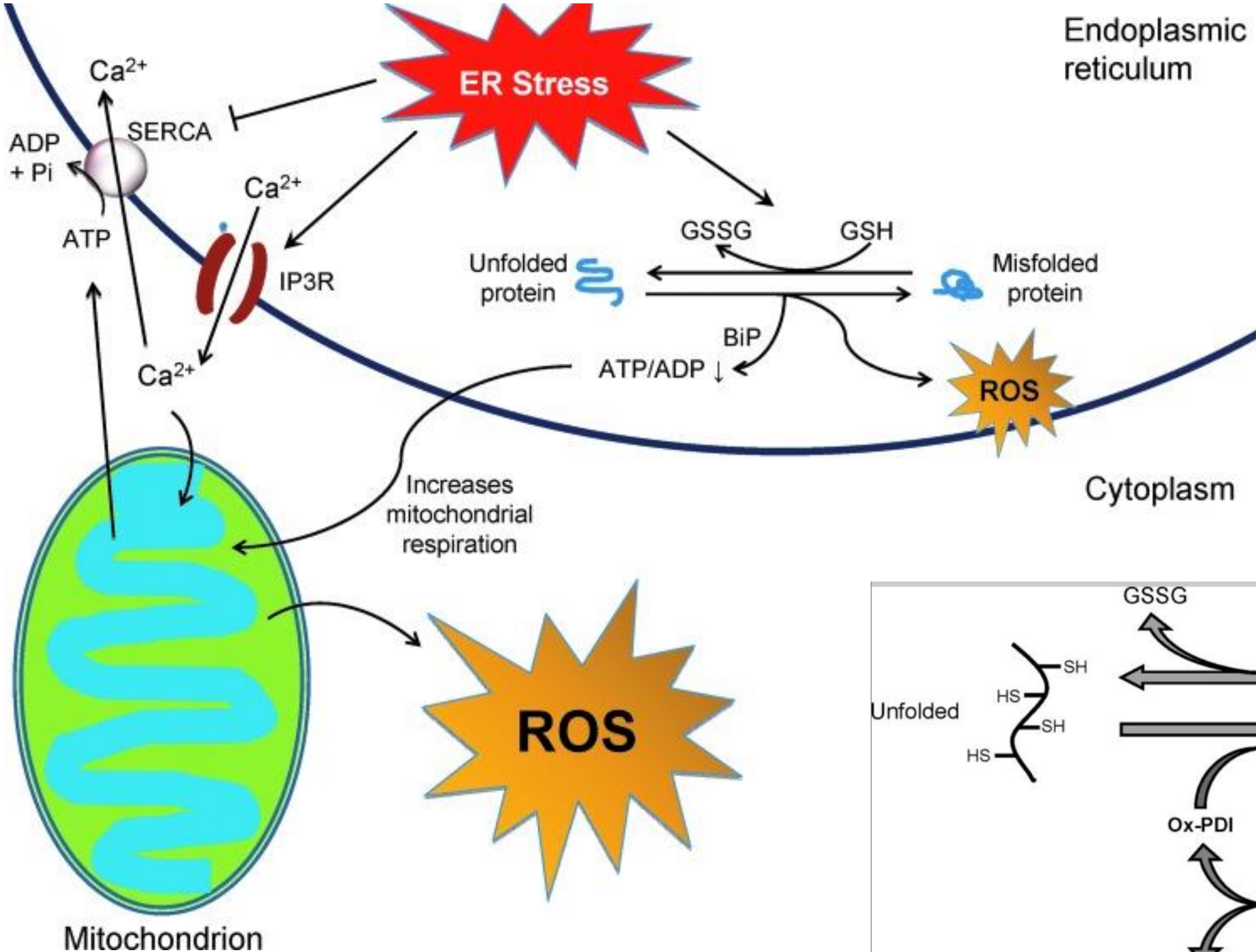
Fig. 1. Types of cell death and their morphological hallmarks. Diagrammatic classification of different types of cell death. PCD: programmed cell death. Morphological features of a) a healthy cell, b) a necrotic cell, c) an apoptotic cell and d) an autophagic cell. (Electron micrograph pictures adapted from ref. [150]. Scale bar: 1 mm.)

Oxidative stress induces apoptosis, necrotic cell death and autophagy via ER stress-mediated DAPK



V. Nikoletopoulou et al. / Biochimica et Biophysica Acta 1833 (2013) 3448–3459

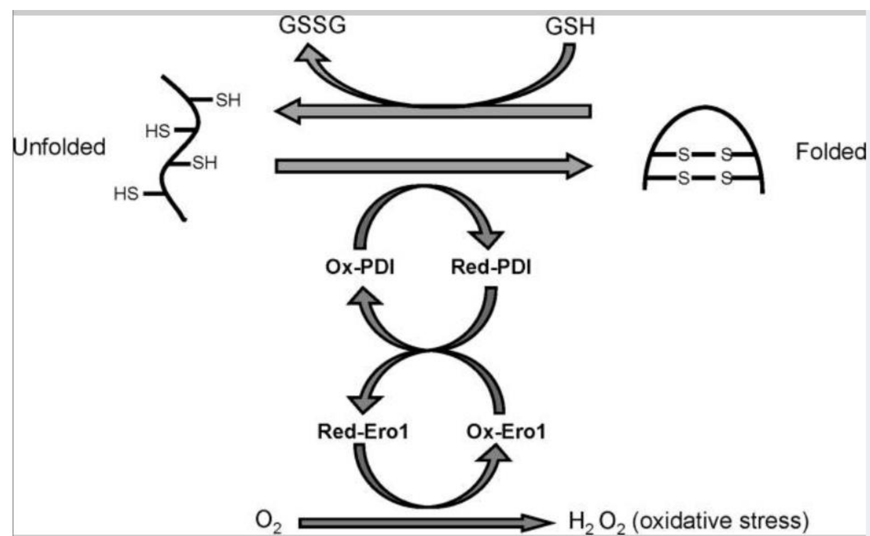
ER stress



ANTIOXIDANTS & REDOX SIGNALING
Volume 21, Number 3, 2014

DOI: 10.1089/ars.2014.5851

The endoplasmic reticulum (ER) is a specialized organelle for the folding and trafficking of proteins, which is highly sensitive to changes in intracellular homeostasis and extracellular stimuli.



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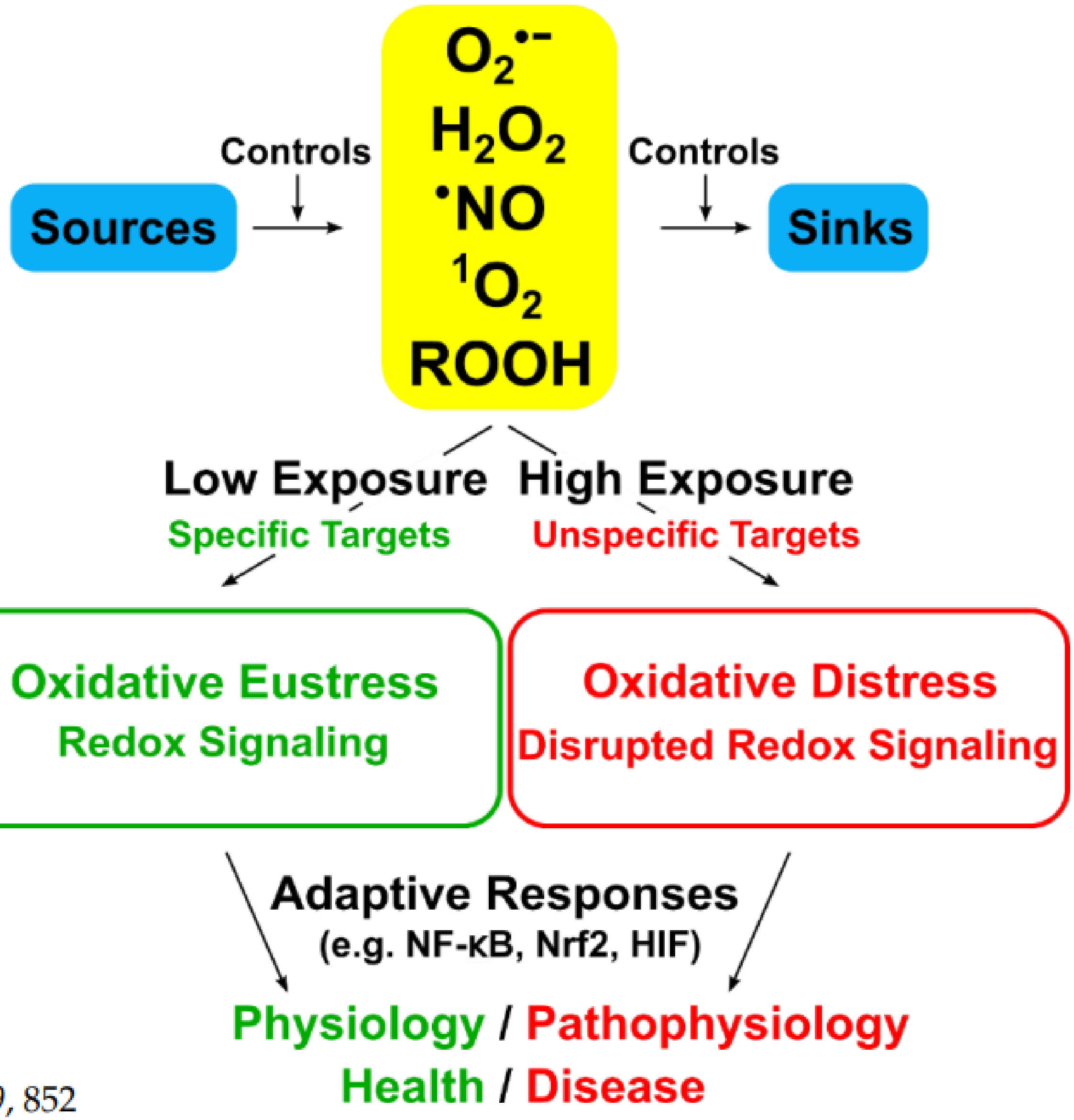
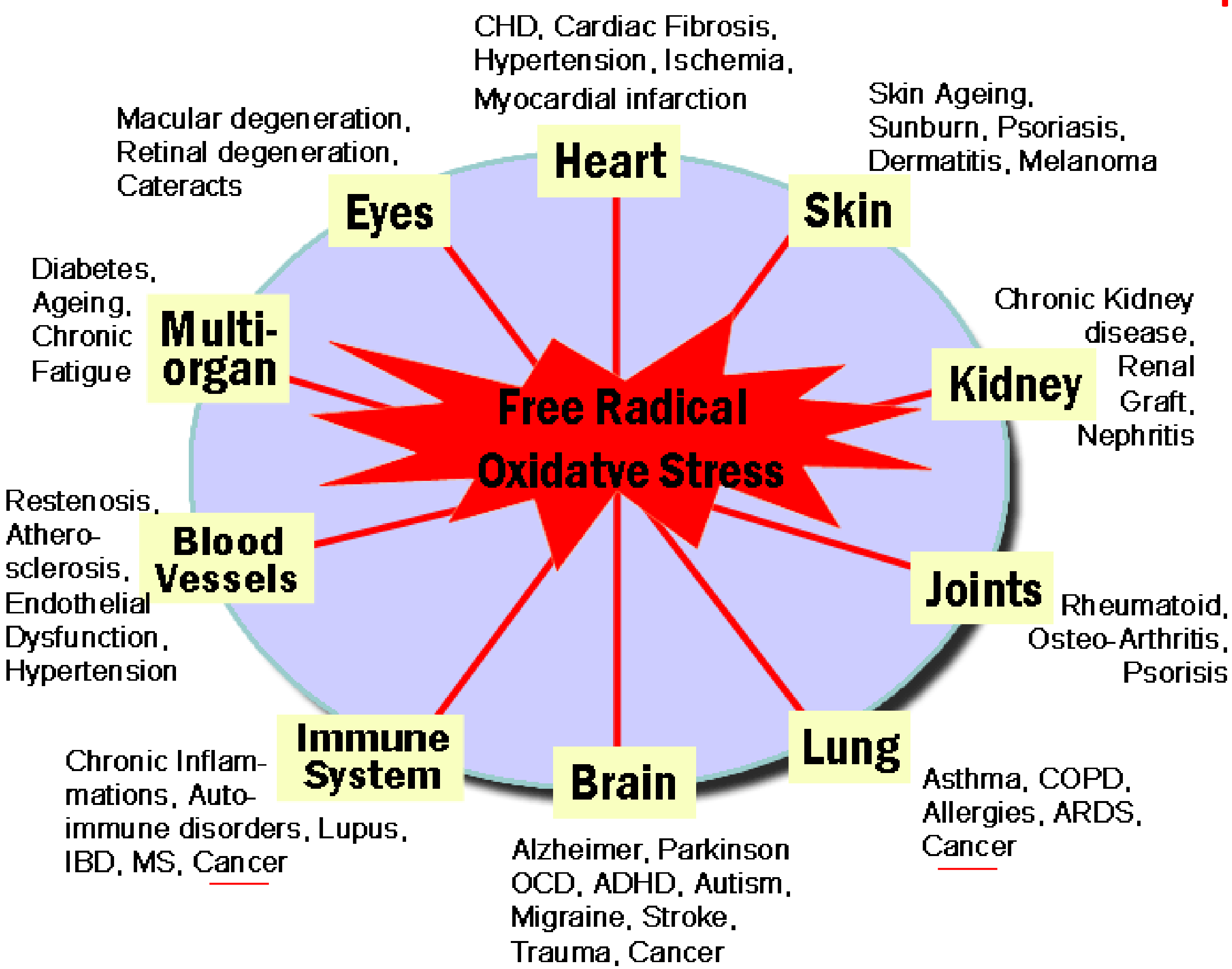
6. Oxidative stress-related diseases

Oxidative stress and its relationship to redox signaling



Antioxidants **2020**, *9*, 852

Oxidative Stress Related Diseases

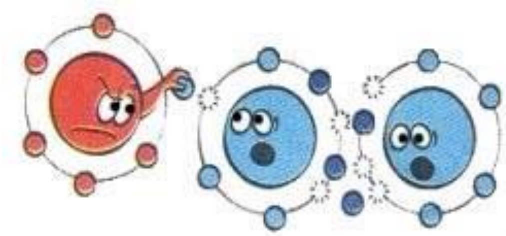


Inflammation-related diseases

-Cancers

-Degenerative diseases

Oxidative stress



Damage to biomolecules

Genetic instability
- Mutation
- Epigenetic change

Adaptive response

Oncogene activation & Tumor suppressor gene inactivation

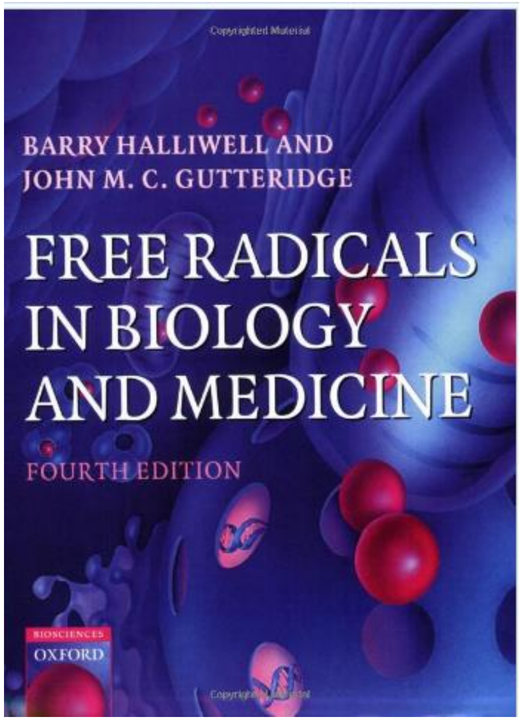
Cancers

Dysfunction/Senescence/Cell Death

Degenerative diseases

(Aging-related diseases)

References



Int. J. Mol. Sci. **2015**, *16*, 193-217; doi:10.3390/ijms16010193

OPEN ACCESS
International Journal of
Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms

Review

Oxidative Stress and Its Significant Roles in Neurodegenerative Diseases and Cancer

Raynoo Thanan [1,2], Shinji Oikawa [3], Yusuke Hiraku [3], Shiho Ohnishi [4], Ning Ma [5], Somchai Pinlaor [2,6], Puangrat Yongvanit [1,2], Shosuke Kawanishi [4] and Mariko Murata [3,*]

1 Department of Biochemistry, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand; E-Mails: rothanan@yahoo.com (R.T.); puangrat@kku.ac.th (P.Y.)
2 Liver Fluke and Cholangiocarcinoma Research Center, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand; E-Mail: mrsomchaip@yahoo.com
3 Department of Environmental and Molecular Medicine, Mie University Graduate School of Medicine,

Review Article

Role of Nitrative and Oxidative DNA Damage in Inflammation-Related Carcinogenesis

Mariko Murata,[1] Raynoo Thanan,[1,2] Ning Ma,[3] and Shosuke Kawanishi[2]

[1] *Department of Environmental and Molecular Medicine, Mie University Graduate School of Medicine, Tsu, 514-8507, Japan*
[2] *Faculty of Pharmaceutical Sciences, Suzuka University of Medical Science, Suzuka, 513-8670, Japan*
[3] *Faculty of Health Science, Suzuka University of Medical Science, Suzuka, 510-0293, Japan*

Correspondence should be addressed to Shosuke Kawanishi, kawanisi@suzuka-u.ac.jp

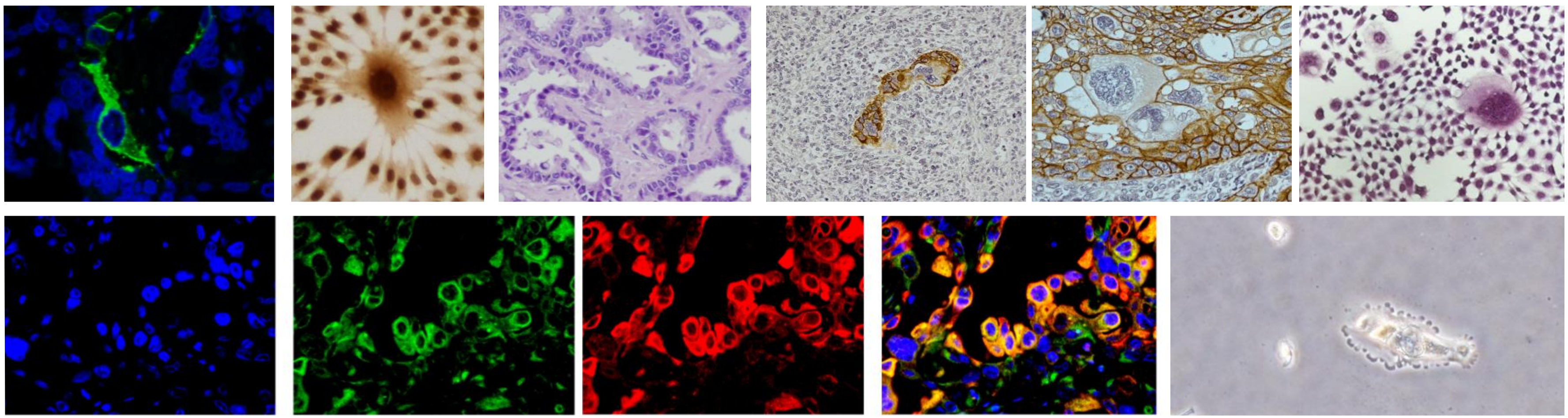
Received 28 July 2011; Accepted 7 October 2011

Academic Editor: Vassilis Gorgoulis

Post test

Example of research on oxidative stress in cancer

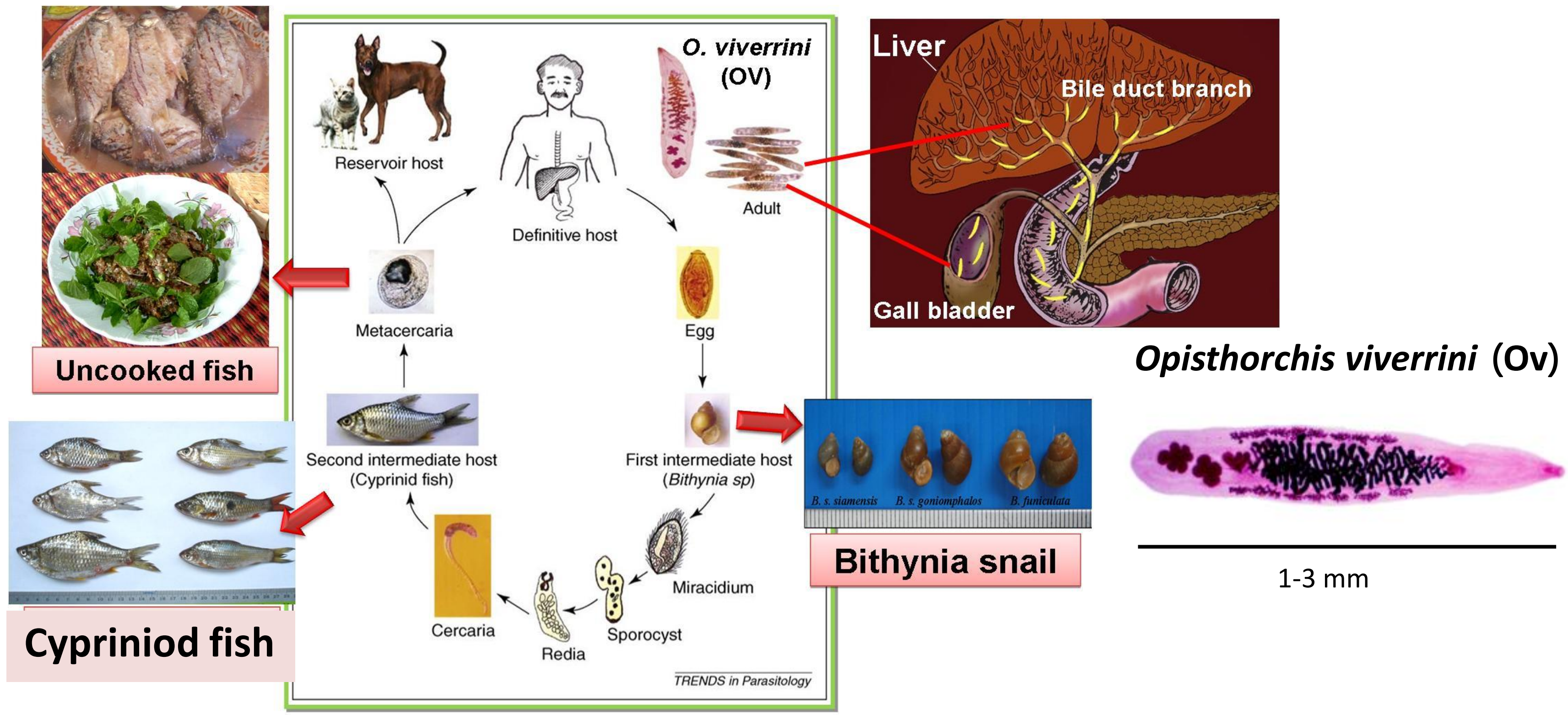
Oxidative stress resistance: an importance factor in cholangiocarcinogenesis



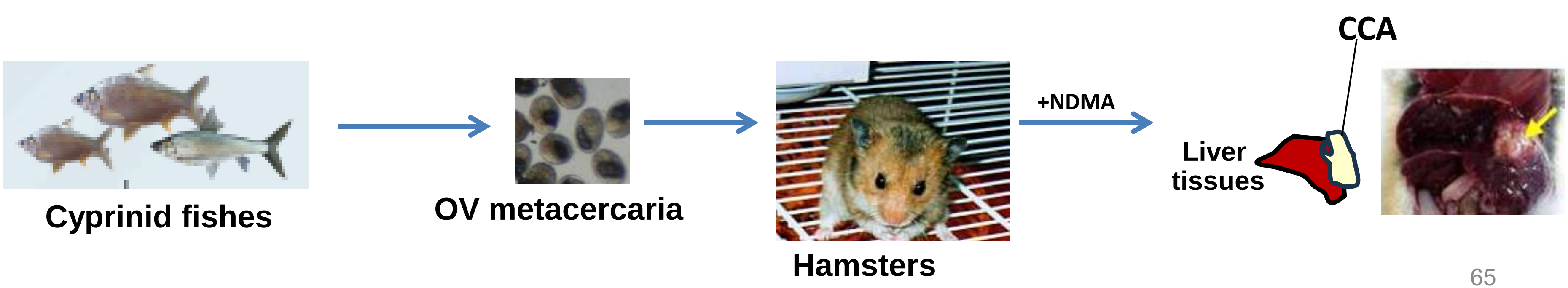
Assoc. Prof. Raynoo Thanan
(Ph.D. Medical Biochemistry)

E-mail: raynoo@kku.ac.th

Liver fluke infection-associated CCA

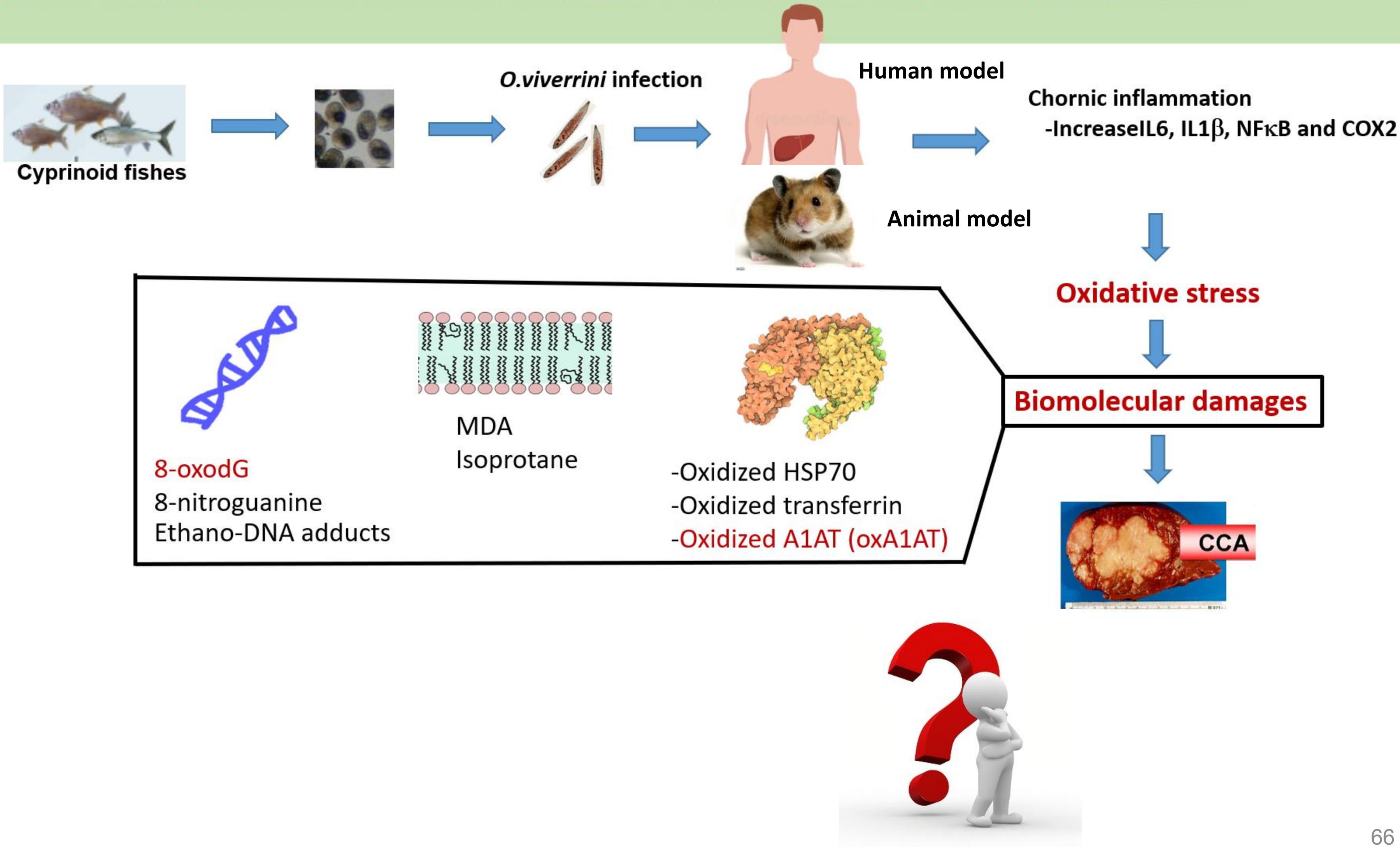


Kaewkes et al., 2003; Sithithaworn et al., 2003; Andrews et al., 2008 , Prakobwong S., et.al, 2010

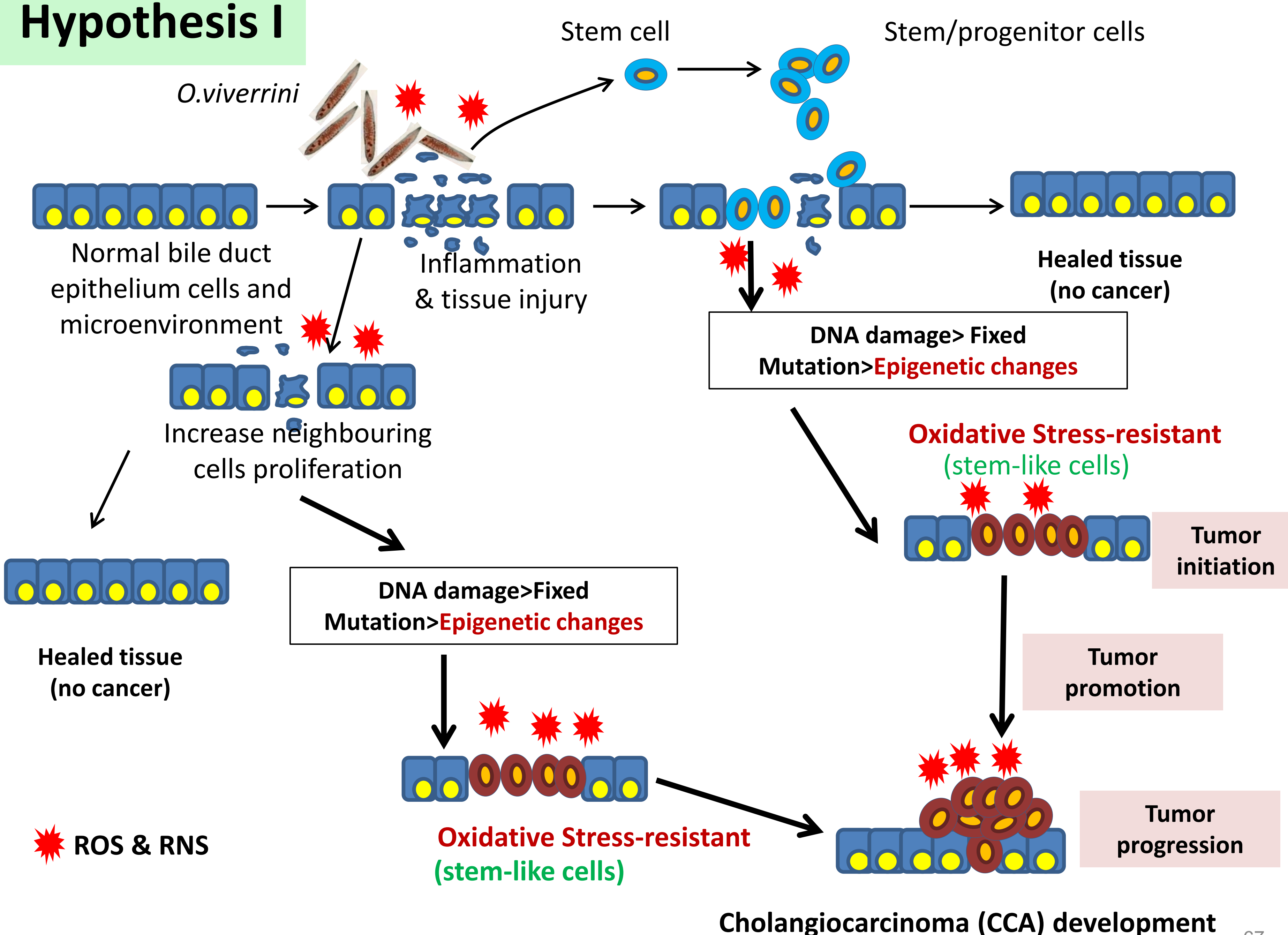


Our previous studies

Liver fluke infection induces oxidative stress via chronic inflammation

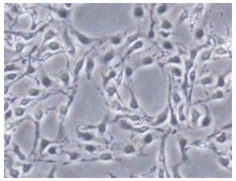


Hypothesis I



Research design I

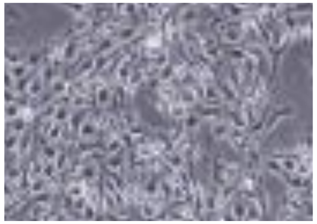
Induction of oxidative stress-resistant cell lines from MMNK1 cells



15 cycles
74 days

~20% confluent → **Expose to 25 μM H_2O_2 every 24 hr** → 80-90% confluent → **Trypsinization** → ~20% confluent

Low oxidative stress induced resistant cell lines (ox-MMNK1-L)



Oxidative stress-resistant properties ↑

Treat with H_2O_2:
- MTT assay

Anti-oxidant enzymes:
- Catalase and SOD2

Tumorigenesis ↑

Growth:
- SRB assay

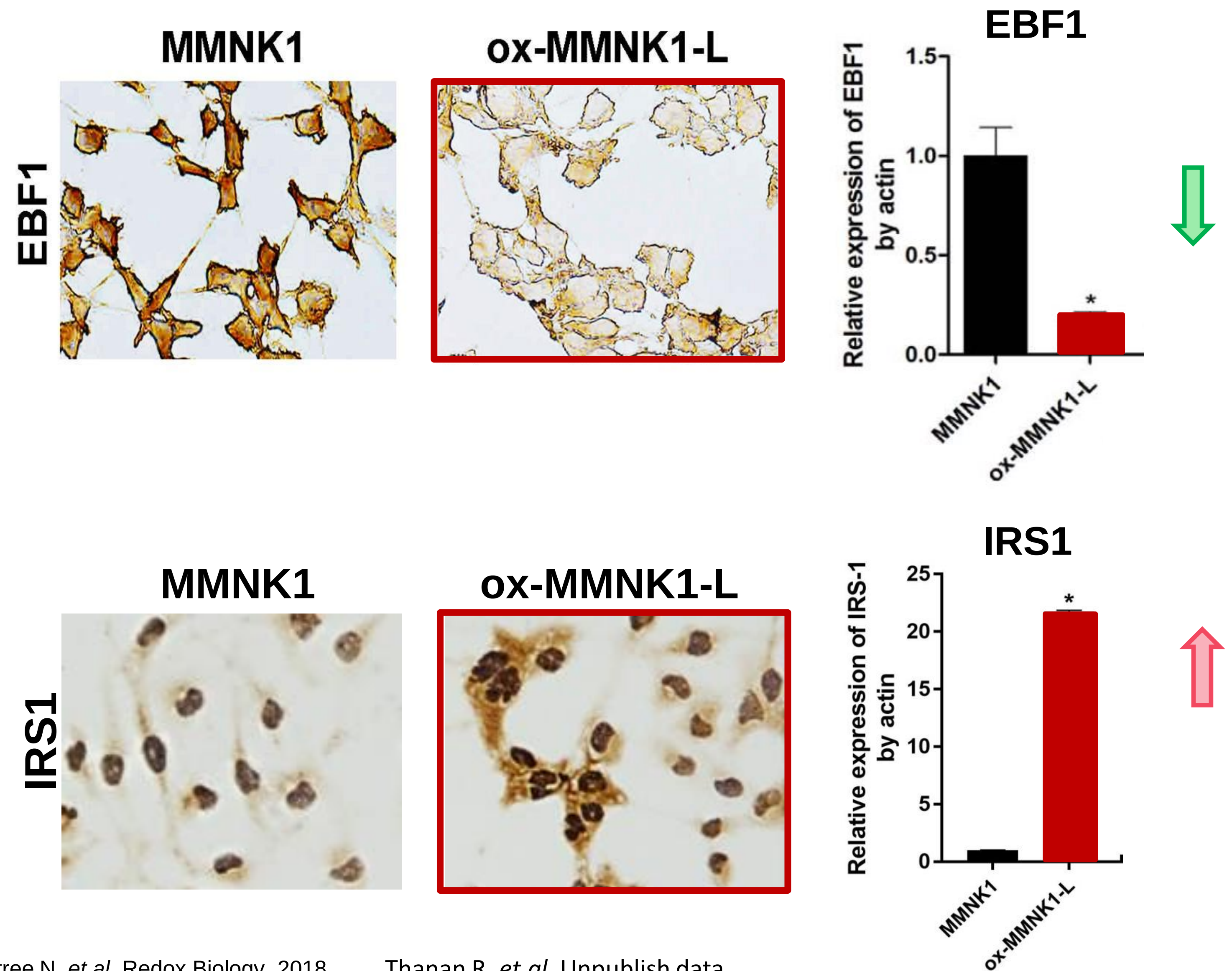
Migration:
- Boyden chamber transwell

Stem cell properties ↑

Stem cell markers:
Oct3/4

Thanan R. *et. al*, BBRC, 2015

Expressions of EBF1 & IRS1 in MMNK1 & ox-MMNK1-L cells



Armartmuntree N. *et.al*, Redox Biology, 2018 Thanan R. *et.al,* Unpublish data

Early B cell factor 1 (EBF1)

Early B cell factor 1 or **EBF1** is a DNA-binding transcription factors. **EBF1** gene locates on chromosome 5q32.

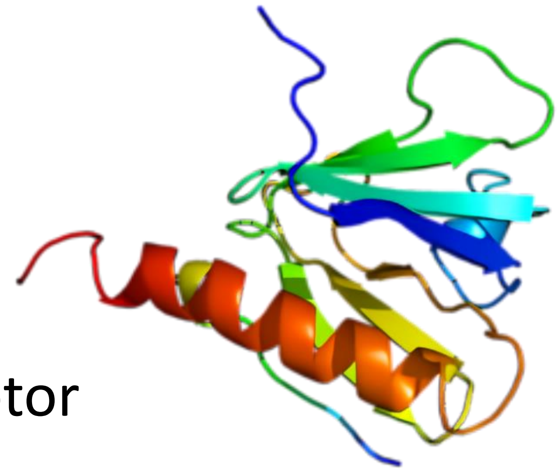
EBF1 is a stem cell-associated transcription factor implicated in the control of hematopoietic and osteo-adipogenesis.

EBF1 is supposed to be the negative regulator of estrogen receptors (ERs).

Down-regulation of EBF1 was found in leukemia and solid cancers, suggesting that **EBF1** may act as a tumor suppressor gene.

Insulin receptor substrate 1 (IRS1)

Insulin receptor substrate 1 or **IRS1** is an intracellular signaling adaptor protein.



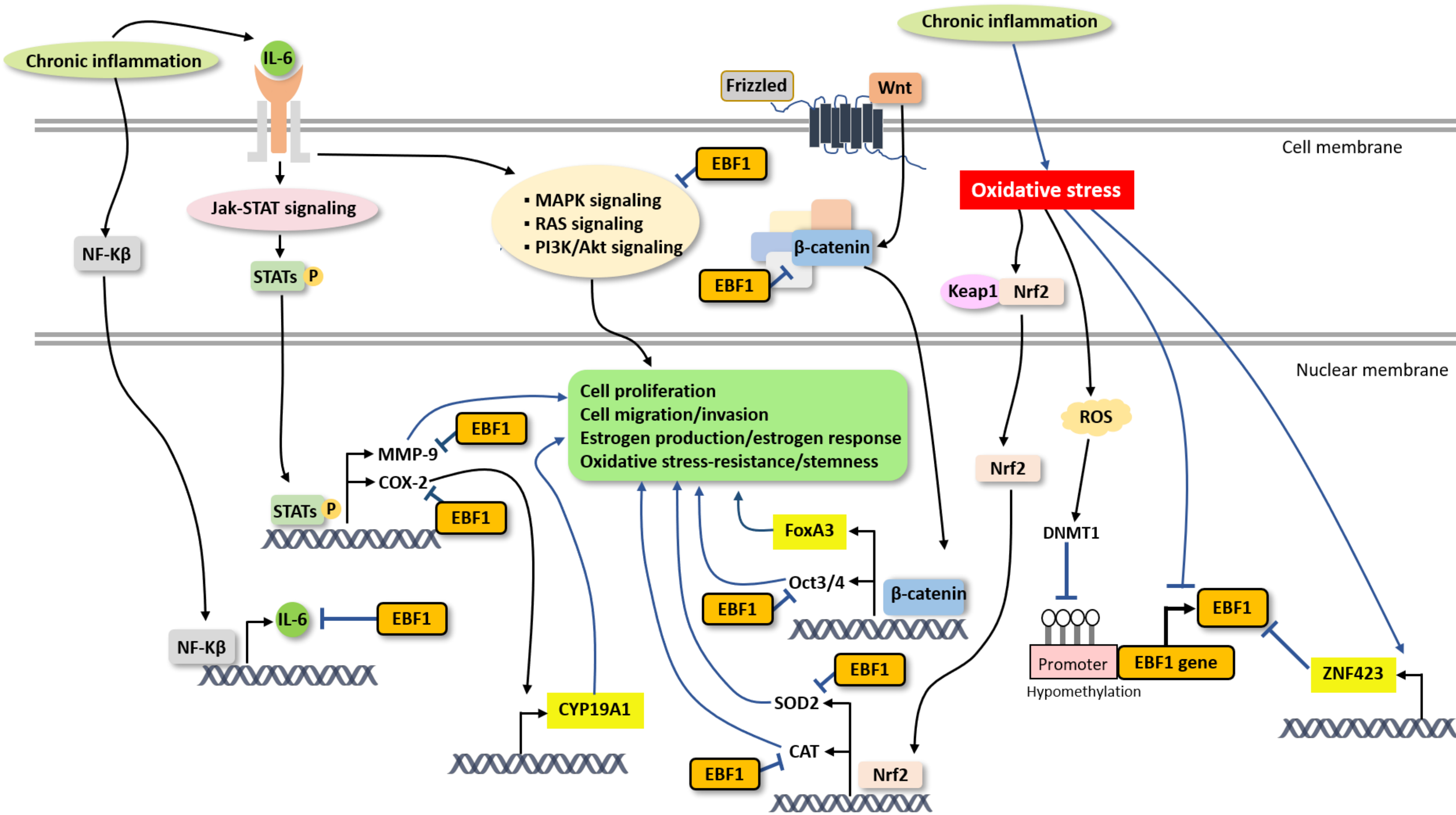
IRS1 gene locates on chromosome 2q36.3.

IRS1 is a major signaling molecule of insulin receptor and insulin like growth factor receptor (IGFR).

IRS1 is widely expressed in normal tissues including muscle, adipocyte, kidney and mammary gland.

Up-regulation of IRS1 was found in leukemia and solid cancers, suggesting that **IRS1** may act as a **oncogene**.

EBF1 acts as a tumor suppressor gene in CCA.



Armartmuntree N. *et.al,* Redox Biology, 2018

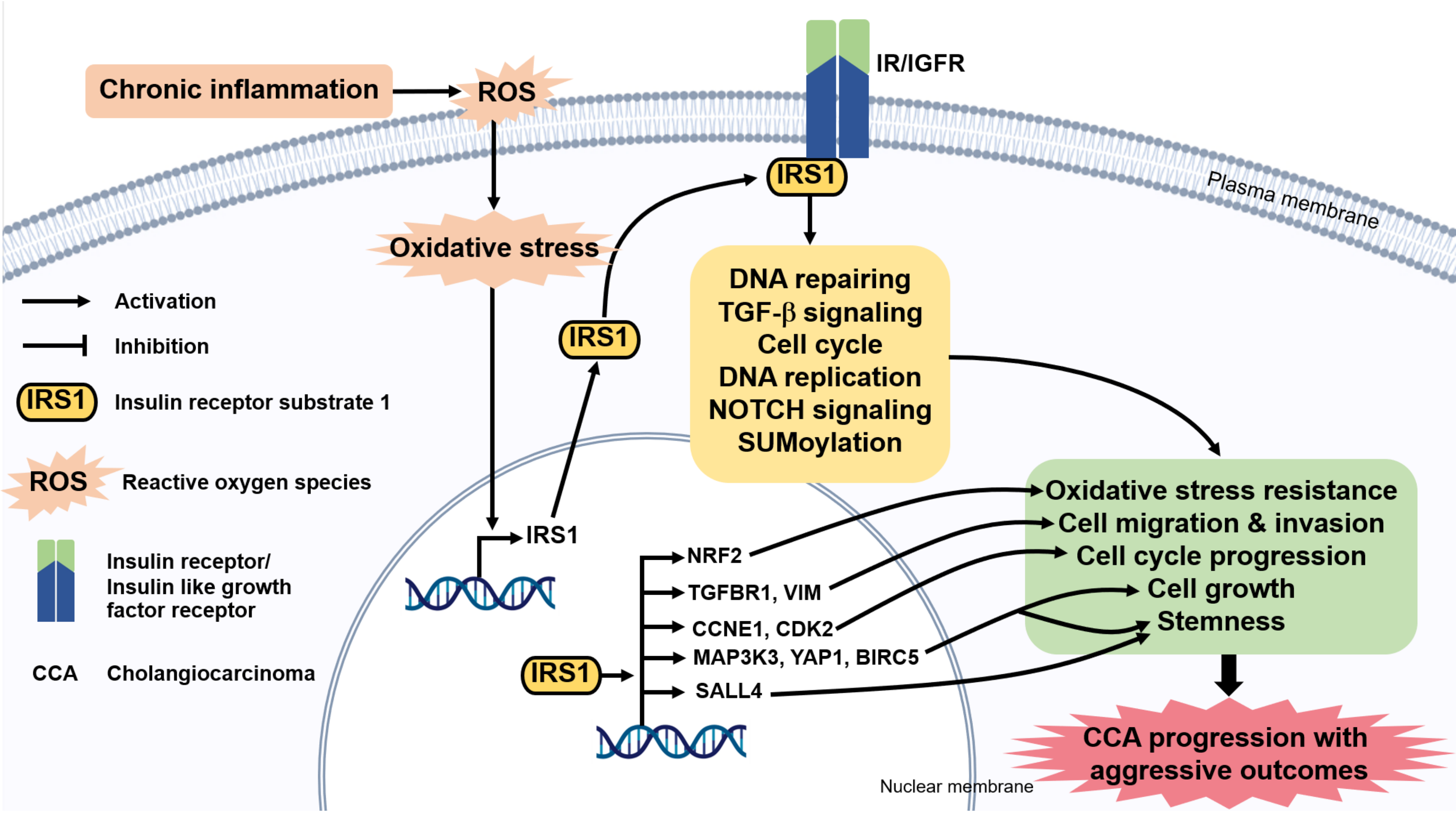
Kaewlert W. *et.al,* Hormone and Cancer, 2018

Chaiprasert T. *et.al,* Biomolecules, 2019

Thanan R. *et.al,* IJMS, 2020

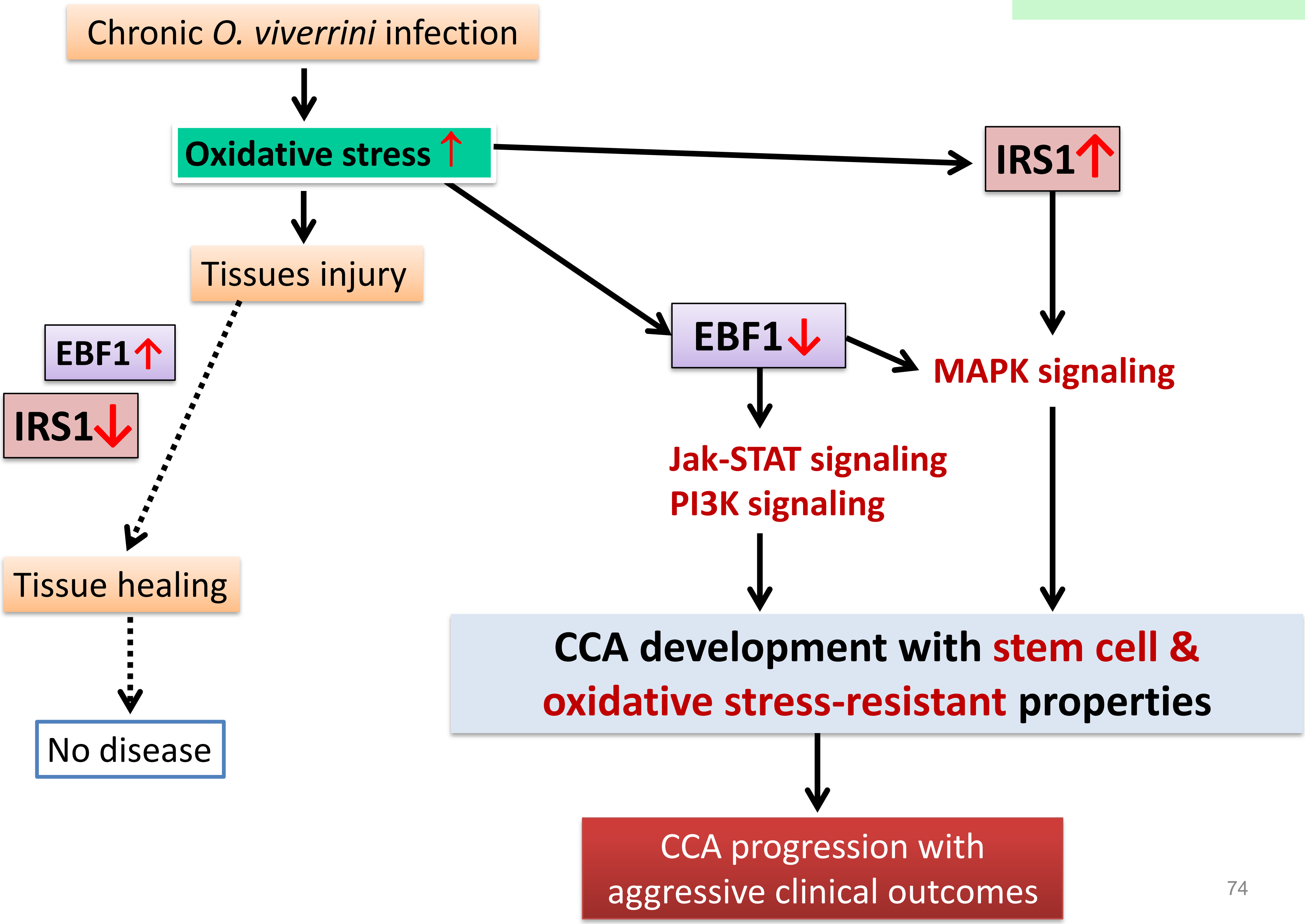
Armartmuntree N. *et.al,* J of Cancer, 2021

IRS1 plays oncogenic roles in CCA.

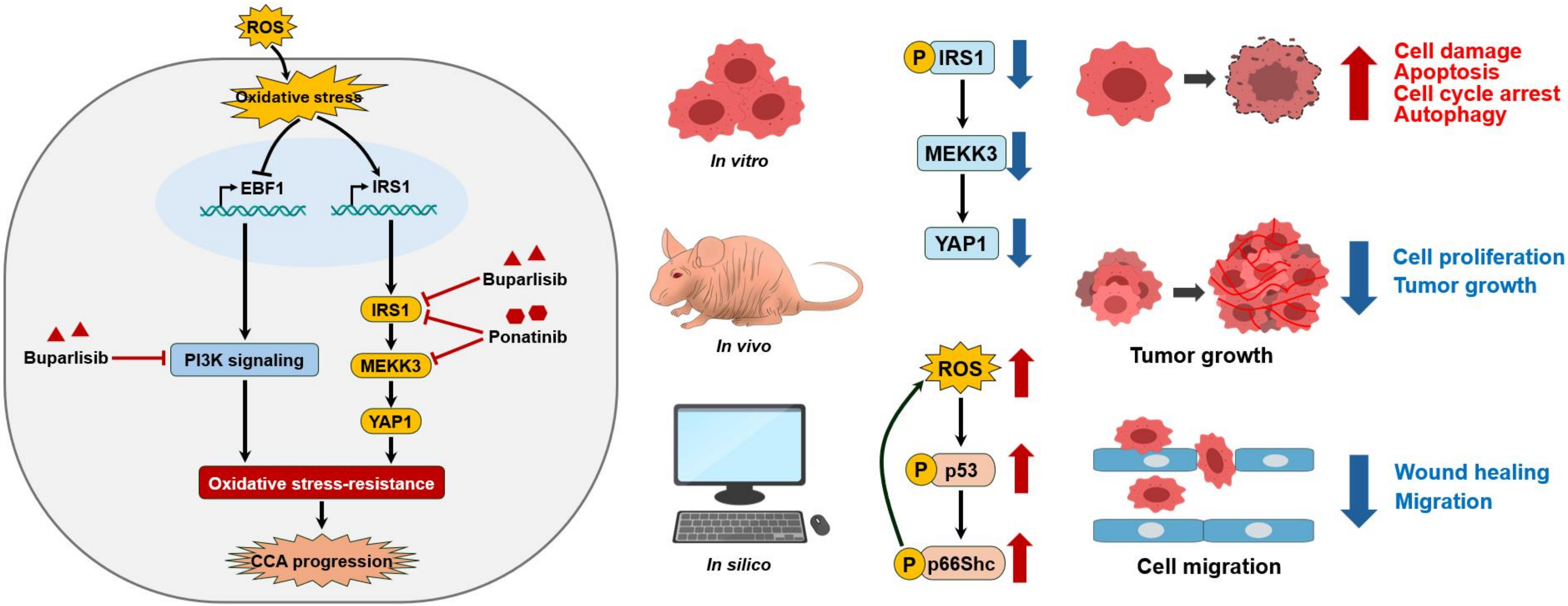


Kaewlert W. *et.al*, IJMS, 2023

Summary II


Chronic O. viverrini infection
Oxidative stress ↑
IRS1↑
Tissues injury
EBF1↓
EBF1↑
IRS1↓
MAPK signaling
Jak-STAT signaling
PI3K signaling
Tissue healing
CCA development with stem cell & oxidative stress-resistant properties
No disease
CCA progression with aggressive clinical outcomes

Buparlisib and ponatinib inhibit aggressiveness of cholangiocarcinoma cells via suppression of IRS1-related pathway by targeting oxidative stress resistance



Kaewlert W. *et.al,* 2025 Biomedicine & Pharmacotherapy