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Invited critical review

Does measurement of oxidative damage to DNA have clinical significance?

Marcus S. Cooke [a,b,*], Ryszard Olinski [c], Mark D. Evans [a]

[a] *Radiation and Oxidative Stress Group, Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, LE2 7LX, UK*

[b] *Department of Genetics, University of Leicester, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, LE2 7LX, UK*

[c] *Department of Clinical Biochemistry, Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, ul. Karlowicza 24, PO-85-092 Bydgoszcz, Poland*

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Abstract

Oxidative damage to DNA is the seemingly inevitable consequence of cellular metabolism. Furthermore, despite protective mechanisms, cellular levels of damage may increase under conditions of oxidative stress, arising from exposure to a variety of physical or chemical insults. Elevated levels of oxidatively damaged DNA have been measured in numerous diseases, and as a result, it has been hypothesised that such damage plays an integral role in the aetiology of that disease. This review examines the validity of this hypothesis, exploring the mechanisms by which oxidative DNA damage may lead to disease. We conclude that further validation of biomarkers of oxidative DNA damage, along with further elucidation of the role of damage in disease, may allow these biomarkers to become potentially useful clinical tools.

Keywords: DNA damage; Disease; Reactive oxygen species; DNA repair

Contents

Abbreviations: ROS, reactive oxygen species; ODD, oxidative DNA damage; 8-OH-Ade, 8-hydroxyadenine; 8-OH-Gua, 8-hydroxyguanine; Tg, thymine glycol; FapyAde, 4,6-diamino-5-formamidopyrimidine; FapyGua, 2,6-diamino-4-hydroxy-5-formamidopyrimidine; 8-OH-dG, 8-hydroxy-2′-deoxyguanosine; 5-OH-Mura, 5-hydroxy-methyluracil; hMTH1, human Mut T homologue 1; 8-OH-dGTP, 8-hydroxy-deoxyguanosine triphosphate; BER, base excision repair; hMYH, human Mut Y homologue; NER, nucleotide excision repair; AP, apurinic–apyrimidinic; hOGG1, human 8-oxoguanine glycosylase 1; HPLC, high performance liquid chromatography; ESCODD, European Standards Committee on DNA Damage; GC-MS, gas chromatography-mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LC-GC-MS, GC-MS with liquid chromatography pre-purification; ELISA, enzyme-linked immunosorbant assay; RIA, radioimmunoassay; LIP, labile iron pool; NSCLC, non-small cell lung cancer; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

* Corresponding author. Radiation and Oxidative Stress Group, Department of Cancer Studies and Molecular Medicine, and Department of Genetics, University of Leicester, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, LE2 7LX, UK. Tel.: +44 116 2525825.
E-mail address: msc5@le.ac.uk (M.S. Cooke).

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1. Free radicals and oxidative stress

Free radicals are defined as any chemical moiety capable of existing with a lone electron in an orbital i.e. an unpaired electron (denoted as .). It is this facet which makes free radicals more reactive than non-radicals, since orbital pairing of electrons increases stability. Reactive oxygen species (ROS) are oxygen containing molecules which may

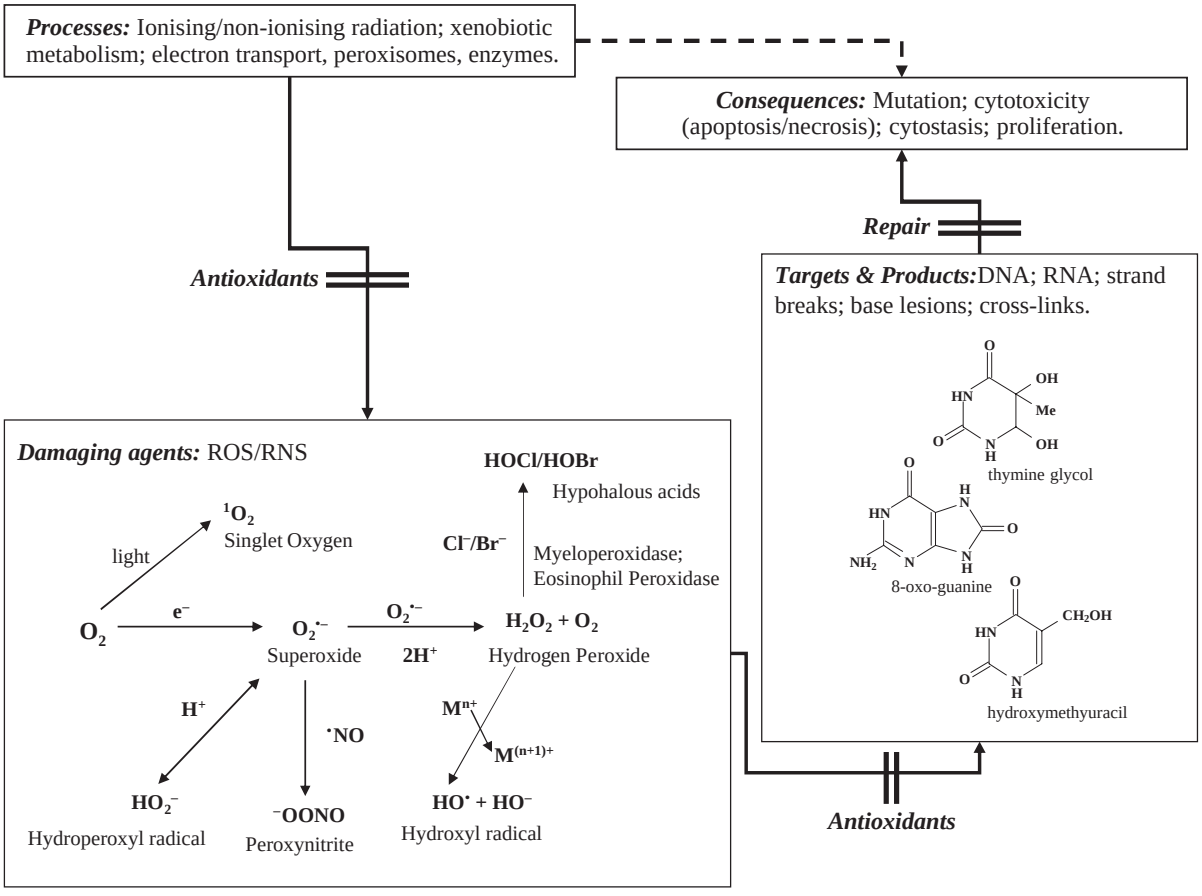

Fig. 1. Biologically relevant reactive oxygen species: sources, cellular consequences and protection. *Sources* — common cellular sources of oxidants are described, along with how ROS and RNS may be formed. M^{n+} and $M^{(n+1)}$ represent reduced and oxidised metal ions. *Cellular consequences*: modified DNA (examples of modified DNA bases shown) can give rise alterations in cellular processes ultimately leading to cytotoxicity, cytostasis, or proliferation. *Protection:* ROS may be intercepted by low molecular weight antioxidants, such as vitamin C and E, or antioxidant enzymes, such as superoxide dismutase (derived from Evans and Cooke, [22]).