Published by iambr.info/AMBR

Open Access Commentary

Oxidative stress: impact in redox biology and medicine

Helmut Sies[1-3]

ABSTRACT

The field of oxidative stress research embraces chemistry, biochemistry, cell biology, physiology and pathophysiology, all the way to medicine and health and disease research. "*Oxidative stress is an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage*" (Sies, H., Jones, D. (2007) in: *Encyclopedia of Stress* (Fink, G., ed.), 2nd Ed., Vol.3, 45-48). The concept of oxidative stress is presented and discussed in context of current developments. Recent research on molecular redox switches governing oxidative stress responses provides further mechanistic insight in redox biology. The fundamental importance of linking redox shifts to phosphorylation/dephosphorylation signaling is being more fully appreciated. The redox relationships by which biological systems are organized have recently been conceptualized under four principles which, together, make up the '*Redox Code*'. On the more practical side, cautious use of terminology and methods is recommended regarding so-called ROS, reactive oxygen species, and RNS, reactive nitrogen species. The major role in antioxidant defense is fulfilled by antioxidant enzymes, not by small-molecule antioxidant compounds.

KEY WORDS: ***Oxidative stress; Redox biology; Medicine***

To cite: Sies H. Oxidative stress: impact in redox biology and medicine. *Arch Med Biomed Res.* 2015;2(4):146-50. doi: 10.4314/ambr.v2i4.6

Publication history
Received: June 30, 2015
Revised: July 5, 2015
Accepted: July 6, 2015

CrossRef Link
http://dx.doi.org/10.4314/ambr.v2i4.6

Correspondence to
Helmut Sies;
sies@uni-duesseldorf.de

INTRODUCTION

The concept of oxidative stress has been introduced in 1985, 30 years ago, and a recent commentary dealt with the merits and pitfalls of this concept[1]. Among the merits is the notion which is elicited by the two terms, namely (i) that aerobic metabolism is a steady-state characterized by a redox balance, as denoted by the term 'oxidative', and (ii) that strains in the balance can occur, as denoted by the term 'stress'. The latter evokes the occurrence of biological stress responses.

Research on oxidative stress responses elucidated the functioning of central master switches, for example NF-kappaB or Nrf2/Keap1, or OxyR in prokaryotes. Much of redox signaling occurs through molecular thiol redox switches, with significance of particularly reactive cysteines in specialized proteins (see Refs[2,3] for recent reviews).

Hydrogen peroxide (H_2O_2) has become known as a normal metabolite under aerobic conditions in living cells[4], occurring at about 10 nM intracellular concentration. A major contributor is

respiratory chain, notably Complexes I and III. Another major source resides in the activity of the various NADPH oxidases. In liver, H_2O_2 is produced at 50 nmol/min/g of tissue, which is about 2 % of total oxygen uptake at steady state. Metabolically generated H_2O_2 emerged from recent research as a central hub in redox signaling and oxidative stress (see[5]).

Regarding pitfalls of the concept, 'oxidative stress' has not always been implicated in full understanding, both in the public perception and in research circles (see below). In research, simply to talk of 'exposing cells or organs to oxidative stress' should be discouraged; instead, the exact molecular conditions need to be identified. Even more important, in transposing redox considerations into medicine, concrete molecular oxidation-reduction descriptions are to be preferred.

A related pitfall is the use of the term 'ROS', which stands for reactive oxygen species, and 'RNS', which stands for reactive nitrogen species, where again the chemical involved should be focused on whenever possible (see Ref.[1] for references). This issue has been dealt with in detail recently in Ref.[6], which serves to guide researchers to appropriate use of free radical research terminology and methodology.

It is worth pointing out that the major burden of antioxidant defense is carried by antioxidant enzymes, not by small-molecular-weight compounds such as antioxidant vitamins[7]. Thus, the patterns of antioxidant enzymes governed by redox sensing and redox signaling deserve more attention.

There are important implications for redox medicine, *e.g.* relating to aging, cell proliferation and cancer, intermediary metabolism (diabetes), nutrition, cardiovascular research, and the circadian rhythm (see Ref.[8] for references).

OXIDATIVE STRESS: UP TO CURRENT DEVELOPMENTS

The concept of oxidative stress has been introduced for research in redox biology and medicine in 1985, now 30 years ago, in an introductory chapter[9] in a book entitled *'Oxidative Stress'*[10]. A concurrent comprehensive review entitled 'Biochemistry of Oxidative Stress' presented the knowledge on prooxidants and antioxidants and their endogenous and exogenous sources and metabolic sinks[11]. A noteworthy insight, early on, was the perception that oxidation-reduction (redox) reactions in living cells are utilized in fundamental processes of redox regulation, collectively termed 'redox signaling' and 'redox control'. A book *'Antioxidant and Redox Regulation of Genes'* highlighted that development at an early stage[12]. The concept of oxidative stress was updated to include the role of redox signaling[13].

Useful as the term 'oxidative stress' may be in research, there has been an inflationary development in research circles and more so in the medical field and, even more than that, in public usage outside scientific endeavors ('over-stressing' the term). This led to a dilution of the meaning, to overuse and even misuse. Cautionary words were published[14] and even explicit criticism was voiced[15-17]. "Over time, the mechanistic basis of the concept was largely forgotten and instead of the oxidative stress hypothesis becoming more precise in terms of molecular targets and mechanism, it became diffuse and nonspecific"[16]. In fact, an 'oxidative stress hypothesis' has not been formulated up to now. If anything, there were implicit deductions: for example, that because of the redox balance concept any single compound, e.g. a small-molecule redox-active vitamin, could alter the totality of the system. Such a view overlooks counter regulation and redundancies in the redox network. There is specificity inherent in the strategies of antioxidant defense[7].

Obviously, a general term, such as oxidative stress, describing a global condition cannot be meant to depict specific spatiotemporal chemical relationships in detail and in specific cells or organ conditions.

These relationships have recently been conceptualized under four principles, which, together, make up the *'Redox Code'* by which biological systems are organized[8]. Given the enormous variety and range of pro-oxidant and antioxidant enzymes and compounds, attempts were made to classify subforms of oxidative stress and to introduce intensity scales ranging from physiological oxidative stress to excessive and toxic oxidative burden[18].

A comprehensive treatment of merits and pitfalls of 'oxidative stress' is to be deferred to an in-depth treatment (in preparation). As mentioned above, it is a challenge to combine the basic chemical notion of oxidation-reduction, including oxygen metabolites (such as the superoxide anion radical, hydrogen peroxide, hydroxyl radical, electronically excited states such as singlet molecular oxygen, as well as the nitric oxide radical and peroxynitrite) with a biological concept, that of stress, introduced by Selye in his research of adaptive responses[19].

Quite often, redox components thought to be centrally important in disease processes are flatly denoted as oxidative stress; this can be found in numerous schemes in the current biomedical literature. The underlying biochemically rigorous foundation may often be missing. This deficiency in scientific stringency pervades also into the analytics: measuring so-called 'total antioxidant capacity (TAC)' in a blood plasma sample will not give meaningful information on the state of the organism and should be discouraged[20]. Rather, individual antioxidant enzyme activities and patterns of antioxidant molecules need to be assessed (see[6,20]).

WHAT IS ATTRACTIVE ABOUT 'OXIDATIVE STRESS'?

Molecular redox switches - The enormously productive field of molecular switches was opened by the discovery of phosphorylation/dephosphorylation serving a mechanism in molecular signaling[21]. The role of molecular *redox switches* came into focus more recently, foremost the dynamic role of cysteines in proteins, opening the field of the redox proteome, currently flourishing because of advances in mass spectrometric and imaging methodology[2,22,23]. A bridge between phosphorylation/dephosphorylation and protein cysteine reduction/oxidation is given by the redox sensitivity of critical cysteinyl residues in protein phosphatases, opening the molecular pathway for signaling cascades as fundamental processes throughout biology.

What was particularly exciting to many researchers was the discovery of master switch systems[24], prominent examples being OxyR in bacteria[25] and NFkB[26] and Nrf2/Keap1[27] in higher organisms. That batteries of enzyme activities are mustered by activation of gene transcription through a 'simple' redox signal is still an exciting strategy. Much of current effort in redox biology is addressed towards these response systems. Obviously, medical and pharmacological intervention attempts are a consequence.

OUTLOOK

More detailed molecular understanding will also deepen the translational impact into biology and medicine; as mentioned above, these aspects are beyond this mini review and will be treated elsewhere. However, it might be mentioned, for example, that viral and bacterial infections are often associated with deficiencies in micronutrients, including the essential trace element, selenium, and the redox-active moiety in selenoproteins[28]. Selenium status may

affect the function of cells in both adaptive and innate immunity. Major diseases, now even diabetes Type 2, are being considered as 'redox disease'[29]. There are close linkages between the Nrf2/Keap1 system and diabetes[30].

Molecular insight will enhance the thrust of the concept of oxidative stress, which is intimately linked to cellular energy balance. Thus, the subcellular compartmentation of redox processes and redox components is being studied at a new level, in mammalian cells as well as in phototrophic organisms[31,32]. New insight from spatiotemporal organization of hydrogen peroxide metabolism[5,8] complements the longstanding interest in hydroperoxide metabolism in mammalian organs[33].

Author affiliations
[1]Institute of Biochemistry and Molecular Biology I, [2]Leibniz Research Institute for Environmental Medicine, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany
[3]College of Science, King Saud University, Riyadh, Saudi Arabia

Acknowledgement: I gratefully acknowledge the input and friendship of many colleagues in shaping ideas in this multidisciplinary field. This includes the many active scientists in this research field, gathered under the umbrella of the Society for Free Radical Research International (SFRRI) and related organisations such as the Oxygen Club of California (OCC). I also am thankful for the research support by the National Foundation of Cancer Research (NFCR), Bethesda, MD, USA, and to the Deutsche Forschungsgemeinschaft and the Alexander-von-Humboldt Foundation.

REFERENCES

1. Sies H. Oxidative stress: a concept in redox biology and medicine. Redox Biol. 2015;4:180-3.
2. Herrmann JM, Becker K, Dick TP. Highlight: dynamics of thiol-based redox switches. *Biol Chem*. 2015;396:385-7
3. Riemer J, Schwarzländer M, Conrad M, Herrmann JM. Thiol switches in mitochondria: operation and physiological relevance. *Biol Chem*. 2015;396:465-82.
4. Sies H, Chance B. The steady state level of catalase compound I in isolated hemoglobin-free perfused rat liver. *FEBS Lett*. 1970;11:172-6.
5. Sies H. Role of metabolic H_2O_2 generation. Redox signaling and oxidative stress. *J Biol Chem*. 2014;289:8735-41.
6. Forman HJ, Augusto O, Brigelius-Flohé R, Dennery PA, Kalyanaraman B, Ischiropoulos H, et al. Even free radicals should follow some rules: a guide to free radical research terminology and methodology. *Free Radic Biol Med*. 2015;78:233-5.
7. Sies H. Strategies of antioxidant defense. 1993. *Eur J Biochem*. 1993;215:213-9.
8. Jones DP, Sies H. The redox code. *Antioxid Redox Signal*. 2015;23:734-46.
9. Sies H. Oxidative stress: introductory remarks. In: 'Oxidative Stress', Sies H ed. Academic Press, London. 1985. 1-8
10. Sies H. Ed. Oxidative Stress. Academic Press, London. 1985. 1-507
11. Sies H. Biochemistry of oxidative stress. *Angew Chem Int Ed Engl*. 1086;25:1058-71.
12. Sen CK, Sies H, Baeuerle PA. eds. Antioxidant and Redox Regulation of Genes. Academic Press, San Diego and London. 2000. 1-562
13. Sies H, Jones DP. Oxidative stress. in: 'Encyclopedia of Stress' (Fink, G., ed.), 2nd Ed., Vol. 3, Elsevier, Amsterdam. 2007. 43-9
14. Sies H. Oxidative stress: introduction. In: 'Oxidative Stress: Oxidants and Antioxidants' (Sies, H., ed.). Academic Press. London. 1991. xv-xxii.
15. Azzi A, Davies KJ, Kelly F. Free radical biology – terminology and critical thinking. *FEBS Lett*. 2004;558:3-6.
16. Levonen A-L, Hill BG, Kansanen E, Zhang J, Darley-Usmar VM. Redox regulation of antioxidants, autophagy, and the response to stress: Implications for electrophile therapeutics. *Free Radic Biol Med*. 2014:71:196-207
17. Lichtenberg D, Pinchuk I. Oxidative stress, the term and the concept. *Biochem Biophys Res Commun*. 2015;461:441-4
18. Lushchak VI. Free radicals, reactive oxygen species, oxidative stress and its

classification. *Chem Biol Interact*. 2014;224C:164-75.
19. Selye H. Stress and disease. *Science*. 1955;122:625-31.
20. Pompella A, Sies H, Wacker R, Brouns F, Grune T, Biesalski HK, et al. The use of total antioxidant capacity as surrogate marker for food quality and ist effect on health is to be discouraged. *Nutrition*. 2014;30:791-3.
21. Fischer EH, Krebs EG. Conversion of phosphorylase-b to phosphorylase-a in muscle extracts. *J Biol Chem*. 1955;216:121-32
22. Go YM, Jones DP. The redox proteome. *J Biol Chem*. 2013;288:26512-20.
23. Groitl B, Jakob U. Thiol-based redox switches. *Biochim Biophys Acta*. 2014;1844:1335-43
24. D'Autréaux B, Toledano MB. ROS as signalling molecules: mechanisms that generate specificity in ROS homeostasis. *Nat Rev Mol Cell Biol*. 2007;8:813-24.
25. Zheng M, Aslund F, Storz G. Identification of the OxyR regulatory disulphide bond by mass spectrometry. *Science*. 1998;279:1718-21.
26. Schreck R, Rieber P, Baeuerle PA. Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF-kappaB transcription factor and HIV-1. *EMBO J*. 1991;10:2247-58.
27. Itoh K, Chiba T, Takahashi S, Ishii T, Igarashi K, Katoh Y, et al. An Nrf2 small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. *Biochem Biophys Res Commun*. 1998;236:313-22
28. Steinbrenner H, Al-Quraishy S, Dkhil MA, Wunderlich F, Sies H. Dietary selenium in adjuvant therapy of viral and bacterial infections. *Adv Nutr*. 2015;6:73-82.
29. Watson JD. Type 2 diabetes as a redox disease. *Lancet*. 2014;383:841-3.
30. Uruno A, Yagishita Y, Yamamoto M. The Keap1-Nrf2 system and diabetes mellitus. *Arch Biochem Biophys*. 2015;566:76-84
31. Schmitt FJ, Renger G, Friedrich T, Kreslavski VD, Zharmukhamedov SK, Los DA, et al. Reactive oxygen species: re-evaluation of generation, monitoring and role in stress-signaling in phototrophic organisms. *Biochim Biophys Acta*. 2014;1837:835-48.
32. del Rio LA. ROS and RNS in plant physiology: an overview. *J Exper Botany*. 2015;66:2827-37
33. Chance B, Sies H, Boveris A. Hydroperoxide metabolism in mammalian organs. *Physiol Revs*. 1979;59:527-605.