ORIGINAL PAPER

Reactive Oxygen Species: Beyond Their Reactive Behavior

Arnaud Tauffenberger[1] · Pierre J. Magistretti[1]

Abstract

Cellular homeostasis plays a critical role in how an organism will develop and age. Disruption of this fragile equilibrium is often associated with health degradation and ultimately, death. Reactive oxygen species (ROS) have been closely associated with health decline and neurological disorders, such as Alzheimer's disease or Parkinson's disease. ROS were first identified as by-products of the cellular activity, mainly mitochondrial respiration, and their high reactivity is linked to a disruption of macromolecules such as proteins, lipids and DNA. More recent research suggests more complex function of ROS, reaching far beyond the cellular dysfunction. ROS are active actors in most of the signaling cascades involved in cell development, proliferation and survival, constituting important second messengers. In the brain, their impact on neurons and astrocytes has been associated with synaptic plasticity and neuron survival. This review provides an overview of ROS function in cell signaling in the context of aging and degeneration in the brain and guarding the fragile balance between health and disease.

Keywords Reactive species · ROS · Hormesis · Homeostasis

Introduction

The cellular functions rely on a variety of extracellular signals and intracellular signaling that function in concert to maintain cellular homeostasis. Most, if not all, cellular processes require considerable energy. Mitochondria are known to fulfill this crucial role, producing the majority of the energy supporting cell growth and homeostasis. However, the dark side of energy production is the formation of reactive oxygen species (ROS) as a by-product by the mitochondria's electron transport chain [1]. Until recently, ROS were essentially considered to be responsible for significant cellular damages [2], causing premature aging and neurodegenerative disorders. Since the 1950s and Harman's *Free-radical theory of aging* [3], a compelling amount of research has investigated how ROS and reactive nitrogen species (RNS) influence disease progression. However, this theory is now being challenged on the basis of considerable evidence suggesting that ROS can act as second messengers. Furthermore, antioxidants that purportedly should antagonize the putative oxidative damage produced ROS have largely been ineffective in preventing disorders in which ROS are the considered as being the cause [4–7]. It is clear that ROS have complex influences on the cells, depending on their concentration. While their role in macromolecular damage and cell death upon loss of redox homeostasis is still a valid model, a mild increase of reactive species triggers various cellular signaling cascades that allow cell growth and survival [8–10]. Recently the concept of hormesis (which can also be dubbed "what does not kill you makes you stronger") has been applied to ROS. Indeed, a contained production of these reactive species promotes stress resistance and longevity in model organisms such as *Caenorhabditis elegans* [11–13], *Drosophila melanogaster* [14, 15] and rodents [16].

Nature of Reactive Species

ROS are, by definition, chemical molecules containing one oxygen atom that, through cellular and extracellular reactions become more reactive than oxygen itself. Reactive species are present in both radical, with and unpaired electron, and non-radical form. An example of ROS is the superoxide

---

✉ Arnaud Tauffenberger
   arnaud.tauffenberger@kaust.edu.sa

✉ Pierre J. Magistretti
   pierre.magistretti@kaust.edu.sa

1   King Abdullah University of Science and Technology,
    Thuwal 23955, Kingdom of Saudi Arabia

anion ($O_2{}^{\bullet-}$) produced as a by-product of the mitochondrial respiration and NADPH oxidase activity. Other ROS include the hydroxyl radicals ($OH^\bullet$) and hydrogen peroxide (H_2O_2) a non-radical species. Another group is called RNS. Nitric oxide ($NO^\bullet$) is produced from L-arginine, by nitric oxide synthase (NOS) and acts a potent second messenger. NO promotes glycolytic metabolism by inhibiting mitochondrial respiration through cytochrome c oxidase and increased AMPK phosphorylation [17, 18]. In parallel, $NO^{\bullet-}$ interacts with superoxide ($O_2{}^{\bullet-}$) to form peroxynitrite ($ONOO^{\bullet-}$) a highly reactive molecule capable of protein nitrosylation and target glutathione, a critical non-enzymatic antioxidant [17, 18].

Sources of Reactive species

Reactive species originate from two primary sources. ROS can either be released as by-products of oxidative metabolism, mainly through mitochondrial respiration or produced during cellular response to xenobiotics or cytokines released as part of a defense mechanism [19, 20] (Fig. 1). Energy production by the mitochondrial electron transport chain accounts for the majority of ROS in the cell. This leak of protons, originating from the oxidation of NADH and $FADH_2$, at the complexes I (NADH dehydrogenase) and III (coenzyme Q and cytochrome c oxidoreductase)
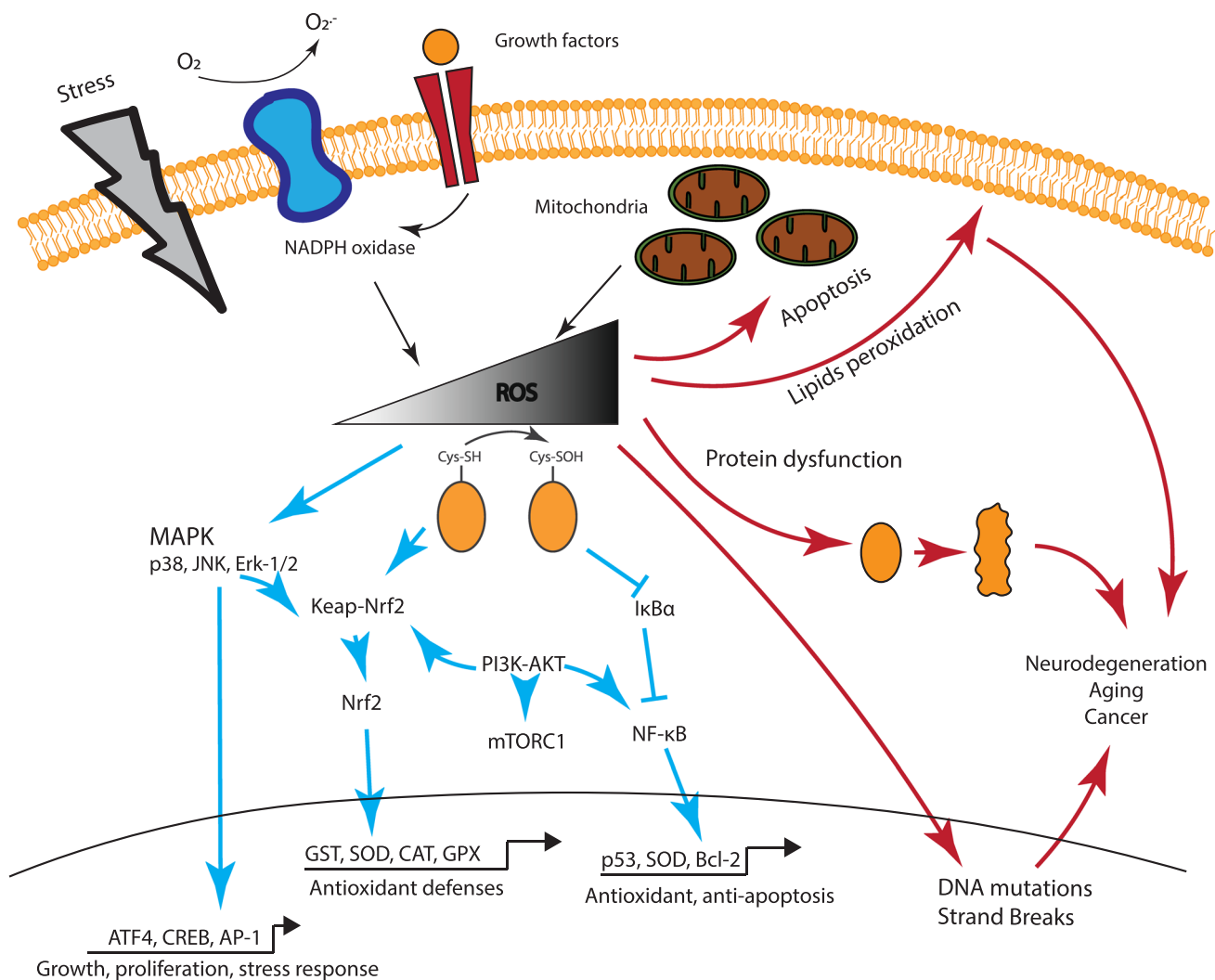

Fig. 1 Schematic representation of the impact of ROS on cellular physiology. Low and Mild ROS level have a large impact on cell signaling, promoting activation of growth signals and kinases (Erk-1/2, PI3K, ATF4 and mTOR) and the transcription of pro-survival (Nrf2, PGC1α) factors. This interactive signaling culminates in the increased expression of antioxidant enzyme (SOD, CAT, GST), the effectors of the survival response. However, increased concentration of ROS disrupt cell signaling and activate pro-apoptotic signals in the mitochondria, as well as lipid peroxidation, protein oxidation and DNA damage. The accumulation of macromolecules and cell damage leads to a wide range of disorders and is associated with accelerate aging

[21, 22] of the electron transport chain, produce a reduced oxygen ion known as superoxide ($O_2^{\bullet-}$) [1].

The second primary source of ROS is the enzyme complex Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Mammals possess seven NADPH oxidases (NOX1–5 and DUOX1–2) that produce ROS in the cytoplasm in response to a variety to stimuli. Initially identified in neutrophils, NADPH oxidase is a membrane-associated enzymatic complex involved in cellular signaling and disease through ROS production in the cytoplasm. Various ligands like TNFα, angiotensin II, PDGF and EGF [23–26] have been associated to NOX-mediated ROS production in response to cellular stimuli such as pathogen invasion, inflammation, growth factors and calcium signaling [27–29]. The complexes produce superoxide radicals and hydrogen peroxide, the latter being more stable and capable of diffusing through the cell membrane [30]. Another significant source of reactive species is the NOS. Present in different isoforms, these complexes are found as a constitutive form in neurons (nNOS or NOS1), as an inducible isoform in glial cells (iNOS or NOS2) and in the endothelial tissue (eNOS or NOS3). NOS produce nitric oxide (NO) that shapes the metabolic profile of the cell by inhibiting the mitochondrial respiration via inhibition of its complex IV (cytochrome c oxidase) and promoting glycolytic activity [31]. However, as mentioned previously, $NO^{\bullet-}$ also reacts with $O_2^{\bullet-}$ to produce peroxynitrite ($ONOO^{\bullet-}$) a reactive specie involved in protein nitration, lipid peroxidation, and DNA damage. In addition of the mitochondria, NOS and NOX, other endogenous, and exogenous, sources have been linked to ROS production, such as the xanthine oxidase, cyclooxygenase, lipoxygenase and the cytochrome P450 [32–35], summarized in Table 1.

Antioxidant Mechanisms

Reactive species concentration need to be maintained at a low level to guarantee a proper cellular environment [36]; mechanisms that ensure antioxidant homeostasis are highly conserved across different species, from the simplest bacteria to humans. The endogenous antioxidant defense is composed of enzymatic and non-enzymatic factors. While the most reactive and toxic form of ROS is the superoxide radical ($O_2^{\bullet-}$), its half-life is relatively short, and it does not diffuse far from the site of production. However, superoxide is quickly converted to hydrogen peroxide (H_2O_2), a more stable form of ROS that can diffuse through membranes. This conversion is mediated by superoxide dismutase (SOD). SODs come in three isoforms, located in different compartments. SOD1 (CuSOD) is mainly cytoplasmic, SOD2 (MnSOD) is located in the mitochondria and SOD3 (CuSOD) is an extracellular isoform. Loss of SOD is associated with an increased level of cellular damage such as lipid peroxidation and protein carbonylation. Mutations in SOD1 are also associated to familial cases of Amyotrophic Lateral Sclerosis (ALS), a devastating neurodegenerative disorder [37]. Although a high concentration of H_2O_2 in the cell can trigger cell death, a low concentration has been linked to several cellular processes related to cell development, growth and survival (see section "ROS Impact on Cell Signaling"). Accumulation of hydrogen peroxide is mainly limited by the activity of other types of enzymes, such as glutathione peroxidase (GPx) and catalases, active in the cytoplasm and the peroxisome respectively. The end-products of these enzymes are water and oxygen. The third ROS converted from H_2O_2, is the Hydroxyl radical ($OH^{\bullet}$), extremely active and oxidizing for lipids, proteins, and DNA [38–40].

Non-enzymatic antioxidants are molecules characterized by their capacity to inactivate reactive species quickly. The most common is glutathione (GSH), involved in both non-enzymatically reduction of ROS as well as being a cofactor in the glutathione peroxidase reduction of peroxides. The

Table 1 Summary of the primary source of ROS

Source of ROS	Response stimuli	Pathway complexes	Main ROS
Mitochondria	Oxidative metabolism	Electron transport chain, NADH	$O_2^{\bullet-}$
NADPH oxidase	Inflammation	NAPDH	$O_2^{\bullet-}$
Xanthine oxidase	Purine catabolism	O_2	$O_2^{\bullet-}$
Nitric oxide synthase	Synaptic activity, inflammation, hypoxia	NADPH	NO, OONO
Peroxisomes	Lipid metabolism (β-oxidation)	NADH, NADPH, $FADH_2$	H_2O_2, $O_2^{\bullet-}$
Cytochrome P450	Clearance of various compounds (hormones, lipids, xenobiotics)	NADPH	$O_2^{\bullet-}$
Lipoxygenases	Arachidonic Acid (PUFA) metabolism	O_2	$O_2^{\bullet-}$
Exogenous stress	Direct peroxidation, increased NOS, DNA damage	UV, environmental toxins, drugs	$O_2^{\bullet-}$, $ONOO^{\bullet-}$, H_2O_2

other primary non-enzymatic antioxidants include metal-binding proteins (albumin, ferritin, myoglobin, and transferrin) able to scavenge free radicals and metals [41–43], and coenzyme Q, a membrane-associated electron carrier involved in electron transfer capable of sustaining significant redox changes [44].

In parallel to the endogenous defense system, natural compounds like the flavonoids, polyphenols (flavonoids, phenolic acids), ascorbic acid (vitamin C) or α-tocopherol have antioxidant capacities that are important to ensure adequate protection against reactive species [45, 46].

ROS Impact on Cell Signaling

At physiological concentrations, ROS have a broad spectrum of roles in signaling as second messengers, with a significant influence on physiological responses (Fig. 1). Several growth factors have been associated with an increase of ROS. Multiple external stimuli, including tumor necrosis factor- (TNF-), growth factors (PDGF, EGF) and cytokines, stimulate the formation of ROS. The main mechanism underlying ROS signaling is the oxidation of thiol (-SH) group on cysteine residues, an amino acid with a low pKa [47]. This reversible action regulates post-translational modification, alteration of protein activity, and relocation in a different cellular compartment.

ROS have been associated with an increased mitogen-activated protein kinases (MAPK) activity [48–50], either through activation of tyrosine kinases or oxidation–reduction of cysteine residues. MAPK are composed of three kinases playing a pivotal role relaying extracellular signals with important outcomes on cell growth, differentiation, development, cell cycle, survival, and cell death [51–53] The main MAPK pathways consist of extracellular signal-related kinases (ERK1/2), the c-Jun N-terminal kinases (JNK), the p38 kinase (p38). These serine/threonine kinases are activated by external stimuli (see above) or by environmental stress [54–57]. ROS influence other tyrosine phosphatases (PTP) and kinases (PK) that are sensitive to redox changes. These include PTEN, phosphatidylinositide 3-kinase (PI3K), AKT, and mTOR [58]. The PI3K–AKT axis plays an important role in cell growth, survival, and protein synthesis. Upon its activation by growth factors (EGF, PDGF) [8], PI3K promotes, and is influenced, by ROS production through NOX and mitochondrial activity, while ROS inactivate phosphatase PTEN [59, 60], PI3K's primary inhibitor. Recently, the emergence of proteomic approaches has allowed identification of over 500 proteins sensitive to redox state, thereby demonstrating ROS capacity to deeply modulate cell activity [61].

ROS also impact the activity of important growth and metabolism-related transcription factors, sensitive to redox changes. The list includes, but is not limited to, Hypoxia Inducible Factor 1α (HIF-1α), NF-kB, Heat Shock Factor 1 (HSF1), p53 and nuclear factor erythroid 2-related factor 2 (Nrf2) [9, 10, 62]. Nrf2 and Kelch-like ECH-associated protein 1 (Keap1) are associated in the cytosol, promoting ubiquitination of Nrf2 and its degradation by the proteasome [63, 64]. However, ROS induce the oxidation of key reactive cysteine on Keap1, promoting the dissociation of Keap1-Nrf2, allowing translocation of the latter to the nucleus. There, Nrf2 engages with antioxidant response elements (ARE) and on the promoter region of antioxidant factors such as the Glutathione *S*-transferase (GST), leading to increased resistance to oxidative stress [65]. Overall, at low or moderate concentrations ROS play a role in signal transduction. They influence a variety of cellular pathways with a crucial impact on cell physiology, metabolism, and survival.

Impact of Reactive Species on the Brain

The brain and, more specifically, neurons are susceptible to oxidative damage because of the high content of lipids and the heavy oxidative metabolism on which they rely [66]. Oxidative damages, through an accumulation of misfolded proteins and loss of antioxidant defenses, have been associated with the aging-mediated loss of functions [67] and neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) [68].

In the brain, the different cell types are not equal regarding their resistance to oxidative stress. Thus glial cells, like astrocytes, are more resilient to oxidative insults, compared to neurons [18]. Similarly, neurons in different anatomical regions also display variability in their capacity to scavenge reactive species. Neurons in the amygdala, the hippocampus, and cerebellar granules cells appear to be the most sensitive [69, 70]. This sensitivity, compared to astrocytes for example, is also due to a low expression of antioxidant mechanisms [71]. Astrocytes synthetize most of the GSH content in the brain, express transcription factors such as Nrf2, at higher levels than neurons [72, 73] and clear ROS more efficiently [71]. Astrocytes release GSH that is either hydrolyzed to cysteine and used as a source for new GSH molecules in neurons via the γ-glutamate-cysteine ligase catalytic (Gclc) and modifier (Gclm) subunits and build antioxidant defense of their own [74–76]. There are several evidences supporting the role of astrocytes in organizing the antioxidant response through the release of cofactors or energy substrates to support neurons metabolism and synaptic activity [77–79]. Recently, some disputed work has shown that mild oxidative stress was able to stimulate astrocytes' antioxidant defense through translocation of Nrf2, and promote neuronal survival [80, 81] but also that astrocytic

ROS influence neuronal metabolism and improve survival [80, 82].

At synapses ROS are associated to long-term potentiation (LTP), to modulate plasticity and memory [83–85]. LTP is produced through high-frequency signals (HSF) resulting in activation of glutamate-activated *N*-methyl-D-aspartate (NMDA) receptors (NMDAR) permeable to calcium (Ca^{2+}). Ca^{2+} entry triggers ROS production by the mitochondria [86] but also promotes nNOS activity [87, 88] through its binding to calmodulin leading to the formation of nitric oxide ($NO^{\bullet-}$). NO acts as a neurotransmitter, associated with synaptic plasticity and synaptic activity regulation through protein *S*-nitrosylation [89–95]. In astrocytes, induction of NOS2 is Ca^{2+} independent and can be triggered by external stimuli such as inflammation (LPS, TNFα, cytokines, Interferon-γ). Interestingly, NOS activity differs between neurons and astrocytes. NO synthetized in glial cells stimulates glycolytic function, while it does not induce a similar effect in neurons, despite similar capacity to inhibit mitochondrial respiration [96]. Besides direct synaptic regulation, ROS modulate the activity of a variety of protein kinases such as ERK, CAMKII, PKA, PKC involved LTP through transcriptional changes and increased number of glutamate (AMPA) transporters [97]. Manipulations aiming to reduce ROS production limit or abrogate LTP, strengthening the view that ROS have a signaling role in the brain [98–100].

The Role of Reactive Species in the Periphery

Immune cells like macrophages and neutrophils release oxygen radicals upon phagocytic activity, potentially leading to tissue damage, yet these immune cells also are endowed with a high antioxidant capacity ROS are required for both innate and adaptive immune mechanisms [101, 102]. Reactive species are necessary for Lipopolysaccharide (LPS)-mediated activation of Toll-like receptor, leading to the production of pro-inflammatory cytokines [103]. Similarly, ROS can activate and maintain activation of lymphocytes (B and T) involved in the adaptive immune system, participating in its fine regulation. Furthermore, recent work has shown that the use of antioxidant can reverse these effects, leading to a deactivation of the immune system [104, 105].

In muscle cells, ROS play an essential role in contraction and adaptation to repetitive efforts [106]. As in other cell types, mitochondria are central for ROS formation; however in muscle cells, also NOX contributes significantly to reactive species formation both at rest and during exercise [107–110], resulting in particular in cell biogenesis through activation of peroxisome proliferator-activated receptor-g coactivator-1α (PGC-1α) [111]. However, excess levels of ROS induce a loss of contractile power that translates into muscle weakness and fatigue [112, 113]. The primary cellular mechanism involves the sustained activation of NF-kB and FoxO, leading to transcription of a degradation-related protein such as C/EBP homology protein (CHOP) [114–116]. Regular activity, however, can promote adaptation and increase muscle capacities (section "Beyond ROS Reactive Behavior").

Reactive Species in Aging and Disease

The principal harmful effect of ROS is observed during aging where a disequilibrium of the redox state is observed. With aging, neuronal metabolism is impaired, mainly through mitochondrial decay, resulting in decreased ATP and NAD^+ production [117, 118]. This decrease, together with a failure in antioxidant defense mechanisms [119] leads to a rise in intracellular ROS-mediated dysfunction [120, 121]. Considerable evidence has demonstrated increased ROS levels in the nervous system of animal models of Alzheimer and Parkinson diseases or Amyotrophic Lateral Sclerosis [122–124]. Upon disruption of the redox homeostasis, ROS cause protein degradation [125–127], DNA damage [128, 129] and lipid peroxidation [130] (Fig. 1).

Accumulation of damage on macromolecules leads to cellular dysfunction, including in muscles and neurons. In tumoral cells, ROS promote stabilization of hypoxia-inducible factor 1α (HIF-1α), which in turn results in tumor survival by promoting angiogenesis and support of glycolytic metabolism [131–134]. Lipid peroxidation promotes inflammation and tissue damage in the heart and cardiovascular dysfunction [135].

Cancer cells are characterized by their "hyper-metabolism" linked to increased production of ROS [136], which is however neutralized by an equivalent increase in antioxidant defenses [137]. However, the role of oxidative stress-sensitive transcription factors such as Nrf2 is complex and depends greatly on the nature of tumors [138–140]. Altogether, it appears that cancer cells need to maintain a tight redox balance to maintain resistance to ROS. Among pro-tumorigenic factors, DNA mutations are associated to significant metabolic changes, that include reduced oxidative phosphorylation (OXPHOS) and increased glycolysis activity. Because ROS are mainly produced through OXPHOS, the diminution of ROS has been shown to promote tumorigenesis. Therefore, it appears that a minimal concentration of ROS is required for tumors to persist, and this concentration needs to be tightly regulated to prevent oxidative damage in cancer cells [141–144]. The high concentration of ROS has been at the center of attempts to develop therapeutic strategies against cancer, but the successes have been very limited or detrimental [145], suggesting that ROS are not a suitable target for therapies.

Beyond ROS Reactive Behavior

Although ROS can have a deleterious effect on cell survival and in disease, their role in cellular physiology is more complex than initially subsumed. As mentioned above, ROS have a substantial impact on cellular signaling via regulation of over 500 redox-sensitive proteins, mainly kinases, and phosphatases that have a crucial effect on cell growth, differentiation and survival (see section "ROS Impact on Cell Signaling"). For example, it has been shown in multiple models that reduction of mitochondrial respiration can has a positive effect on longevity, in part due to a mild increase in ROS production. Caloric restriction is known to promote longevity and delay neurodegeneration: several observations suggest that ROS such as H_2O_2 could be linked to the positive outcome on longevity by activating anti-aging pathways such as the AMPK [146–148], while we and others have revealed a link between the protective effect of L-lactate against oxidative stress and ROS production [149, 150].

During moderate and repeated exercise, the production of ROS by muscle cells has a profound positive effect. Indeed it has been shown that a low concentration of H_2O_2 can increase muscle contractibility [151, 152]. A mild ROS increase can stimulate the expression of antioxidant enzymes, including GSH, but also SOD, CAT, and GPX. Endurance exercise, through a ROS-dependent mechanism, also reduces DNA damage [153] and increases insulin sensitivity [154]. This dose-dependent effect also translates into a long-term growth of the muscle fibers through activation of several signaling pathways such as AMPK, p38MAPK, and PGC-1α [155–157]. Interestingly, the use of exogenous antioxidant, through diet reduces the impact of ROS on muscle adaptation to exercise [158–160].

The latter observation is consistent with the role of preconditioning to ischemia as a protective strategy. Although, re-perfusion of tissue after hypoxia results in a dramatic ROS elevation and tissues damage, a small and short period of ischemia followed by reperfusion can produce protective effects, through ROS dependent mechanisms [161, 162].

Conclusion

Reactive species are more complex than was initially thought. As of today, it appears that the equilibrium between pro-oxidant and antioxidant factors drives cellular physiology in multiple organs and organisms. While an excessive production of ROS has a dramatic negative effects on survival, a mild oxidative environment can produce a variety of positive outcomes crucial for biological organisms to survive and adapt. Therefore a better understanding of reactive species targets and effects, is necessary to target interventional strategies to improve major health-related issues.

Compliance with Ethical Standards

References

1. Murphy MP (2009) How mitochondria produce reactive oxygen species. Biochem J 417:1–13. https://doi.org/10.1042/BJ20081386

2. Halliwell B (2006) Oxidative stress and neurodegeneration: where are we now? J Neurochem 97:1634–1658. https://doi.org/10.1111/j.1471-4159.2006.03907.x

3. Harman D (1956) Aging: a theory based on free radical and radiation chemistry. J Gerontol 11:298–300

4. Ristow M (2014) Unraveling the truth about antioxidants. Nat Med 20:709–711. https://doi.org/10.1038/nm.3624

5. Ristow M, Schmeisser S (2011) Extending life span by increasing oxidative stress. Free Radic Biol Med 51:327–336. https://doi.org/10.1016/j.freeradbiomed.2011.05.010

6. Yun J, Finkel T (2014) Mitohormesis. Cell Metab 19:757–766. https://doi.org/10.1016/j.cmet.2014.01.011

7. Cox CS, McKay SE, Holmbeck MA et al (2018) Mitohormesis in mice via sustained basal activation of mitochondrial and antioxidant signaling. Cell Metab 28(5):776–786.e5. https://doi.org/10.1016/j.cmet.2018.07.011

8. Bäumer AT, Freyhaus Ten H, Sauer H et al (2008) Phosphatidylinositol 3-kinase-dependent membrane recruitment of Rac-1 and p47phox is critical for alpha-platelet-derived growth factor receptor-induced production of reactive oxygen species. J Biol Chem 283:7864–7876. https://doi.org/10.1074/jbc.M704997200

9. Chandel NS, Chandel NS, McClintock DS et al (2000) Reactive oxygen species generated at mitochondrial complex III stabilize hypoxia-inducible factor-1alpha during hypoxia: a mechanism

of O$_2$ sensing. J Biol Chem 275:25130–25138. https://doi.org/10.1074/jbc.M001914200

10. Ahn S-G, Thiele DJ (2003) Redox regulation of mammalian heat shock factor 1 is essential for Hsp gene activation and protection from stress. Genes Dev 17:516–528. https://doi.org/10.1101/gad.1044503

11. Tissenbaum HA (2010) A mitochondrial superoxide signal triggers increased longevity in Caenorhabditis elegans. PLoS Biol 8:e1000556. https://doi.org/10.1371/journal.pbio.1000556

12. Kim SK (2009) Deletion of the mitochondrial superoxide dismutase sod-2 extends lifespan in Caenorhabditis elegans. PLoS Genet 5:e1000361. https://doi.org/10.1371/journal.pgen.1000361

13. Schulz TJ, Zarse K, Voigt A et al (2007) Glucose restriction extends Caenorhabditis elegans life span by inducing mitochondrial respiration and increasing oxidative stress. Cell Metab 6:280–293. https://doi.org/10.1016/j.cmet.2007.08.011

14. Owusu-Ansah E, Song W, Perrimon N (2013) Muscle mitohormesis promotes longevity via systemic repression of insulin signaling. Cell 155:699–712. https://doi.org/10.1016/j.cell.2013.09.021

15. Obata F, Fons CO, Gould AP (2018) Early-life exposure to low-dose oxidants can increase longevity via microbiome remodelling in Drosophila. Nat Commun 9:975. https://doi.org/10.1038/s41467-018-03070-w

16. Lapointe J, Hekimi S (2008) Early mitochondrial dysfunction in long-lived Mclk1+/− mice. J Biol Chem 283:26217–26227. https://doi.org/10.1074/jbc.M803287200

17. Bolaños JP, Heales SJ, Peuchen S et al (1996) Nitric oxide-mediated mitochondrial damage: a potential neuroprotective role for glutathione. Free Radic Biol Med 21:995–1001. https://doi.org/10.1016/s0891-5849(96)00240-7

18. Bolaños JP, Almeida A, Stewart V et al (1997) Nitric oxide-mediated mitochondrial damage in the brain: mechanisms and implications for neurodegenerative diseases. J Neurochem 68:2227–2240. https://doi.org/10.1046/j.1471-4159.1997.68062227.x

19. Finkel T (2011) Signal transduction by reactive oxygen species. J Cell Biol 194:7–15. https://doi.org/10.1083/jcb.201102095

20. Starkov AA (2008) The role of mitochondria in reactive oxygen species metabolism and signaling. Ann N Y Acad Sci 1147:37–52. https://doi.org/10.1196/annals.1427.015

21. Barja G (1999) Mitochondrial oxygen radical generation and leak: sites of production in states 4 and 3, organ specificity, and relation to aging and longevity. J Bioenerg Biomembr 31:347–366

22. Muller FL, Liu Y, Van Remmen H (2004) Complex III releases superoxide to both sides of the inner mitochondrial membrane. J Biol Chem 279:49064–49073. https://doi.org/10.1074/jbc.M407715200

23. Bae YS, Kang SW, Seo MS et al (1997) Epidermal growth factor (EGF)-induced generation of hydrogen peroxide. Role in EGF receptor-mediated tyrosine phosphorylation. J Biol Chem 272:217–221

24. Lo YY, Cruz TF (1995) Involvement of reactive oxygen species in cytokine and growth factor induction of c-fos expression in chondrocytes. J Biol Chem 270:11727–11730. https://doi.org/10.1074/jbc.270.20.11727

25. Rajagopalan S, Kurz S, Münzel T et al (1996) Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J Clin Invest 97:1916–1923. https://doi.org/10.1172/JCI118623

26. Sundaresan M, Yu ZX, Ferrans VJ et al (1995) Requirement for generation of H$_2$O$_2$ for platelet-derived growth factor signal transduction. Science 270:296–299. https://doi.org/10.1126/science.270.5234.296

27. Quagliaro L, Piconi L, Assaloni R et al (2003) Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. Diabetes 52:2795–2804. https://doi.org/10.2337/diabetes.52.11.2795

28. Inoguchi T, Li P, Umeda F et al (2000) High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C-dependent activation of NAD(P)H oxidase in cultured vascular cells. Diabetes 49:1939–1945. https://doi.org/10.2337/diabetes.49.11.1939

29. Bedard K, Krause K-H (2007) The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. Physiol Rev 87:245–313. https://doi.org/10.1152/physrev.00044.2005

30. Cardoso AR, Chausse B, da Cunha FM et al (2012) Mitochondrial compartmentalization of redox processes. Free Radic Biol Med 52:2201–2208. https://doi.org/10.1016/j.freeradbiomed.2012.03.008

31. Almeida A, Moncada S, Bolaños JP (2004) Nitric oxide switches on glycolysis through the AMP protein kinase and 6-phosphofructo-2-kinase pathway. Nat Cell Biol 6:45–51. https://doi.org/10.1038/ncb1080

32. Lipton P (1999) Ischemic cell death in brain neurons. Physiol Rev 79:1431–1568. https://doi.org/10.1152/physrev.1999.79.4.1431

33. Yue Z, Zhang X, Yu Q et al (2018) Cytochrome P450-dependent reactive oxygen species (ROS) production contributes to Mn$_3$O$_4$ nanoparticle-caused liver injury. RSC Adv 8:37307–37314. https://doi.org/10.1039/C8RA05633A

34. Berry CE, Hare JM (2004) Xanthine oxidoreductase and cardiovascular disease: molecular mechanisms and pathophysiological implications. J Physiol 555:589–606. https://doi.org/10.1113/jphysiol.2003.055913

35. Zangar R (2004) Mechanisms that regulate production of reactive oxygen species by cytochrome P450. Toxicol Appl Pharmacol 199:316–331. https://doi.org/10.1016/j.taap.2004.01.018

36. Rahman K (2007) Studies on free radicals, antioxidants, and cofactors. CIA 2:219–236

37. Rosen DR, Siddique T, Patterson D et al (1993) Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature 362:59–62. https://doi.org/10.1038/362059a0

38. Calabrese V (2004) Increased expression of heat shock proteins in rat brain during aging: relationship with mitochondrial function and glutathione redox state. Mech Ageing Dev 125:325–335. https://doi.org/10.1016/j.mad.2004.01.003

39. Rodrigues Siqueira I, Fochesatto C, da Silva Torres IL et al (2005) Aging affects oxidative state in hippocampus, hypothalamus and adrenal glands of Wistar rats. Life Sci 78:271–278. https://doi.org/10.1016/j.lfs.2005.04.044

40. Hamilton ML, van Remmen H, Drake JA et al (2001) Does oxidative damage to DNA increase with age? Proc Natl Acad Sci U S A 98:10469–10474. https://doi.org/10.1073/pnas.171202698

41. Plantier J-L, Duretz V, Devos V et al (2016) Comparison of antioxidant properties of different therapeutic albumin preparations. Biologicals 44:226–233. https://doi.org/10.1016/j.biologicals.2016.04.002

42. Kreutzer U, Jue T (2004) Role of myoglobin as a scavenger of cellular NO in myocardium. Am J Phys Heart Circ Phys 286:H985–H991. https://doi.org/10.1152/ajpheart.00115.2003

43. Guan H, Yang H, Yang M et al (2017) Mitochondrial ferritin protects SH-SY5Y cells against H$_2$O$_2$-induced oxidative stress and modulates α-synuclein expression. Exp Neurol 291:51–61. https://doi.org/10.1016/j.expneurol.2017.02.001

44. Navas P, Villalba JM, de Cabo R (2007) The importance of plasma membrane coenzyme Q in aging and stress responses.

Mitochondrion 7:S34–S40. https://doi.org/10.1016/j.mito.2007.02.010

45. Chan PH (2001) Reactive oxygen radicals in signaling and damage in the ischemic brain. J Cereb Blood Flow Metab 21:2–14. https://doi.org/10.1097/00004647-200101000-00002

46. Bouayed J, Bohn T (2010) Exogenous antioxidants—double-edged swords in cellular redox state: health beneficial effects at physiologic doses versus deleterious effects at high doses. Oxidative Med Cell Longev 3:228–237. https://doi.org/10.4161/oxim.3.4.12858

47. Groitl B, Jakob U (2014) Thiol-based redox switches. Biochim Biophys Acta 1844:1335–1343. https://doi.org/10.1016/j.bbapap.2014.03.007

48. Kamata H, Kamata H, Honda S-I et al (2005) Reactive oxygen species promote TNFalpha-induced death and sustained JNK activation by inhibiting MAP kinase phosphatases. Cell 120:649–661. https://doi.org/10.1016/j.cell.2004.12.041

49. Ruffels J, Griffin M, Dickenson JM (2004) Activation of ERK1/2, JNK and PKB by hydrogen peroxide in human SH-SY5Y neuroblastoma cells: role of ERK1/2 in H_2O_2-induced cell death. Eur J Pharmacol 483:163–173. https://doi.org/10.1016/j.ejphar.2003.10.032

50. Guyton KZ, Guyton KZ, Liu Y et al (1996) Activation of mitogen-activated protein kinase by H_2O_2. Role in cell survival following oxidant injury. J Biol Chem 271:4138–4142. https://doi.org/10.1074/jbc.271.8.4138

51. Brown MD, Sacks DB (2009) Protein scaffolds in MAP kinase signalling. Cell Signal 21:462–469. https://doi.org/10.1016/j.cellsig.2008.11.013

52. Winter-Vann AM, Johnson GL (2007) Integrated activation of MAP3Ks balances cell fate in response to stress. J Cell Biochem 102:848–858. https://doi.org/10.1002/jcb.21522

53. Ravingerová T, Barancík M, Strnisková M (2003) Mitogen-activated protein kinases: a new therapeutic target in cardiac pathology. Mol Cell Biochem 247:127–138. https://doi.org/10.1023/a:1024119224033

54. Junttila MR, Li S-P, Westermarck J (2008) Phosphatase-mediated crosstalk between MAPK signaling pathways in the regulation of cell survival. FASEB J 22:954–965. https://doi.org/10.1096/fj.06-7859rev

55. Ichijo H (1999) From receptors to stress-activated MAP kinases. Oncogene 18:6087–6093. https://doi.org/10.1038/sj.onc.1203129

56. Ramos JW (2008) The regulation of extracellular signal-regulated kinase (ERK) in mammalian cells. Int J Biochem Cell Biol 40:2707–2719. https://doi.org/10.1016/j.biocel.2008.04.009

57. Bogoyevitch MA, Ngoei KRW, Zhao TT et al (2010) c-Jun N-terminal kinase (JNK) signaling: recent advances and challenges. Biochim Biophys Acta Proteins Proteomics 1804:463–475. https://doi.org/10.1016/j.bbapap.2009.11.002

58. Wang Y, Branicky R, Noë A, Hekimi S (2018) Superoxide dismutases: dual roles in controlling ROS damage and regulating ROS signaling. J Cell Biol 217:1915–1928. https://doi.org/10.1083/jcb.201708007

59. Leslie NR, Bennett D, Lindsay YE et al (2003) Redox regulation of PI 3-kinase signalling via inactivation of PTEN. EMBO J 22:5501–5510. https://doi.org/10.1093/emboj/cdg513

60. Kwon J, Lee S-R, Yang K-S et al (2004) Reversible oxidation and inactivation of the tumor suppressor PTEN in cells stimulated with peptide growth factors. Proc Natl Acad Sci U S A 101:16419–16424. https://doi.org/10.1073/pnas.0407396101

61. Weerapana E, Wang C et al (2010) Quantitative reactivity profiling predicts functional cysteines in proteomes. Nature 468:790–795. https://doi.org/10.1038/nature09472

62. Paul S, Ghosh S, Mandal S et al (2018) NRF2 transcriptionally activates the heat shock factor 1 promoter under oxidative stress and affects survival and migration potential of MCF7 cells. J Biol Chem 293:19303–19316. https://doi.org/10.1074/jbc.RA118.003376

63. Nguyen T, Sherratt PJ, Pickett CB (2003) Regulatory mechanisms controlling gene expression mediated by the antioxidant response element. Annu Rev Pharmacol Toxicol 43:233–260. https://doi.org/10.1146/annurev.pharmtox.43.100901.140229

64. Kim KC, Kang KA, Zhang R et al (2010) Up-regulation of Nrf2-mediated heme oxygenase-1 expression by eckol, a phlorotannin compound, through activation of Erk and PI3K/Akt. Int J Biochem Cell Biol 42:297–305. https://doi.org/10.1016/j.biocel.2009.11.009

65. Itoh K, Chiba T, Takahashi S et al (1997) An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. Biochem Biophys Res Commun 236:313–322

66. Magistretti PJ, Allaman I (2015) A cellular perspective on brain energy metabolism and functional imaging. Neuron 86:883–901. https://doi.org/10.1016/j.neuron.2015.03.035

67. Castelli V, Benedetti E, Antonosante A et al (2019) Neuronal cells rearrangement during aging and neurodegenerative disease: metabolism, oxidative stress and organelles dynamic. Front Mol Neurosci 12:217–213. https://doi.org/10.3389/fnmol.2019.00132

68. Jellinger KA (2010) Basic mechanisms of neurodegeneration: a critical update. J Cell Mol Med 14(3):457–487. https://doi.org/10.1111/j.1582-4934.2010.01010.x

69. McCormack AL, Thiruchelvam M, Manning-Bog AB et al (2002) Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. Neurobiol Dis 10:119–127. https://doi.org/10.1006/nbdi.2002.0507

70. Wilde GJ, Pringle AK, Wright P, Iannotti F (1997) Differential vulnerability of the CA1 and CA3 subfields of the hippocampus to superoxide and hydroxyl radicals in vitro. J Neurochem 69:883–886. https://doi.org/10.1046/j.1471-4159.1997.69020883.x

71. Dringen R, Kussmaul L, Gutterer JM et al (1999) The glutathione system of peroxide detoxification is less efficient in neurons than in astroglial cells. J Neurochem 72:2523–2530. https://doi.org/10.1046/j.1471-4159.1999.0722523.x

72. Bell KFS, Al-Mubarak B, Martel M-AE et al (2015) Neuronal development is promoted by weakened intrinsic antioxidant defences due to epigenetic repression of Nrf2. Nat Commun 6:1–15. https://doi.org/10.1038/ncomms8066

73. Jimenez-Blasco D, Santofimia-Castaño P, Gonzalez A et al (2015) Astrocyte NMDA receptors' activity sustains neuronal survival through a Cdk5-Nrf2 pathway. Cell Death Differ 22:1877–1889. https://doi.org/10.1038/cdd.2015.49

74. Dringen R, Kranich O, Hamprecht B (1997) The gamma-glutamyl transpeptidase inhibitor acivicin preserves glutathione released by astroglial cells in culture. Neurochem Res 22:727–733. https://doi.org/10.1023/a:1027310328310

75. Yin B, Barrionuevo G, Weber SG (2017) Mitochondrial GSH systems in CA1 pyramidal cells and astrocytes react differently during oxygen-glucose deprivation and reperfusion. ACS Chem Neurosci 9:738–748. https://doi.org/10.1021/acschemneuro.7b00369

76. Baxter PS, Hardingham GE (2016) Adaptive regulation of the brain's antioxidant defences by neurons and astrocytes. Free Radic Biol Med 100:147–152. https://doi.org/10.1016/j.freeradbiomed.2016.06.027

77. Panatier A, Vallée J, Haber M et al (2011) Astrocytes are endogenous regulators of basal transmission at central synapses. Cell 146:785–798. https://doi.org/10.1016/j.cell.2011.07.022

78. Pellerin L, Bouzier-Sore A-K, Aubert A et al (2007) Activity-dependent regulation of energy metabolism by astrocytes: an update. Glia 55:1251–1262. https://doi.org/10.1002/glia.20528

79. Pellerin L, Magistretti PJ (1994) Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc Natl Acad Sci U S A 91:10625–10629

80. Bell KF, Al-Mubarak B, Fowler JH et al (2011) Mild oxidative stress activates Nrf2 in astrocytes, which contributes to neuroprotective ischemic preconditioning. Proc Natl Acad Sci U S A 108:E1–E2. https://doi.org/10.1073/pnas.1015229108

81. Haskew-Layton RE, Payappilly JB, Smirnova NA et al (2010) Controlled enzymatic production of astrocytic hydrogen peroxide protects neurons from oxidative stress via an Nrf2-independent pathway. Proc Natl Acad Sci U S A 107:17385–17390. https://doi.org/10.1073/pnas.1003996107

82. Vicente-Gutierrez C, Bonora NX, Bobo-Jimenez V et al (2019) Astrocytic mitochondrial ROS modulate brain metabolism and mouse behaviour. Nat Metab 1:201–211. https://doi.org/10.1038/s42255-018-0031-6

83. Bliss TV, Lomo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232:331–356. https://doi.org/10.1113/jphysiol.1973.sp010273

84. Markram H, Lübke J, Frotscher M, Sakmann B (1997) Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science 275:213–215. https://doi.org/10.1126/science.275.5297.213

85. Castellani GC, Quinlan EM, Cooper LN, Shouval HZ (2001) A biophysical model of bidirectional synaptic plasticity: dependence on AMPA and NMDA receptors. Proc Natl Acad Sci U S A 98:12772–12777. https://doi.org/10.1073/pnas.201404598

86. Reynolds IJ, Hastings TG (1995) Glutamate induces the production of reactive oxygen species in cultured forebrain neurons following NMDA receptor activation. J Neurosci 15:3318–3327

87. Garthwaite J, Charles SL, Chess-Williams R (1988) Endothelium-derived relaxing factor release on activation of NMDA receptors suggests role as intercellular messenger in the brain. Nature 336:385–388. https://doi.org/10.1038/336385a0

88. Brenman JE, Chao DS, Gee SH et al (1996) Interaction of nitric oxide synthase with the postsynaptic density protein PSD-95 and alpha1-syntrophin mediated by PDZ domains. Cell 84:757–767. https://doi.org/10.1016/s0092-8674(00)81053-3

89. Hardingham N, Fox K (2006) The role of nitric oxide and GluR1 in presynaptic and postsynaptic components of neocortical potentiation. J Neurosci 26:7395–7404. https://doi.org/10.1523/JNEUROSCI.0652-06.2006

90. Lu YF, Kandel ER, Hawkins RD (1999) Nitric oxide signaling contributes to late-phase LTP and CREB phosphorylation in the hippocampus. J Neurosci 19:10250–10261

91. Rudkouskaya A, Sim V, Shah AA et al (2010) Long-lasting inhibition of presynaptic metabolism and neurotransmitter release by protein S-nitrosylation. Free Radic Biol Med 49:757–769. https://doi.org/10.1016/j.freeradbiomed.2010.05.032

92. Segieth J, Getting SJ, Biggs CS, Whitton PS (1995) Nitric oxide regulates excitatory amino acid release in a biphasic manner in freely moving rats. Neurosci Lett 200:101–104. https://doi.org/10.1016/0304-3940(95)12088-l

93. Steinert JR, Robinson SW, Tong H et al (2011) Nitric oxide is an activity-dependent regulator of target neuron intrinsic excitability. Neuron 71:291–305. https://doi.org/10.1016/j.neuron.2011.05.037

94. Choi YB, Lipton SA (2000) Redox modulation of the NMDA receptor. Cell Mol Life Sci 57:1535–1541

95. Blaise G, Gauvin D, Gangal M, Authier S (2005) Nitric oxide, cell signaling and cell death. Toxicology 208:177–192. https://doi.org/10.1016/j.tox.2004.11.032

96. Almeida A, Almeida J, Bolaños JP, Moncada S (2001) Different responses of astrocytes and neurons to nitric oxide: the role of glycolytically generated ATP in astrocyte protection. Proc Natl Acad Sci U S A 98:15294–15299. https://doi.org/10.1073/pnas.261560998

97. Elgersma Y, Silva AJ (1999) Molecular mechanisms of synaptic plasticity and memory. Curr Opin Neurobiol 9:209–213

98. Klann E (1998) Cell-permeable scavengers of superoxide prevent long-term potentiation in hippocampal area CA1. J Neurophysiol 80:452–457. https://doi.org/10.1152/jn.1998.80.1.452

99. Knapp LT, Klann E (2002) Potentiation of hippocampal synaptic transmission by superoxide requires the oxidative activation of protein kinase C. J Neurosci 22:674–683

100. Knapp LT, Klann E (2002) Role of reactive oxygen species in hippocampal long-term potentiation: contributory or inhibitory? J Neurosci Res 70:1–7. https://doi.org/10.1002/jnr.10371

101. Kamiński MM, Röth D, Krammer PH, Gülow K (2013) Mitochondria as oxidative signaling organelles in T-cell activation: physiological role and pathological implications. Arch Immunol Ther Exp 61:367–384. https://doi.org/10.1007/s00005-013-0235-0

102. West AP, Koblansky AA, Ghosh S (2006) Recognition and signaling by Toll-like receptors. Annu Rev Cell Dev Biol 22:409–437. https://doi.org/10.1146/annurev.cellbio.21.122303.115827

103. Chandel NS, Trzyna WC, McClintock DS, Schumacker PT (2000) Role of oxidants in NF-κB activation and TNF-α gene transcription induced by hypoxia and endotoxin. J Immunol 165:1013–1021. https://doi.org/10.4049/jimmunol.165.2.1013

104. Sena LA, Li S, Jairaman A et al (2013) Mitochondria are required for antigen-specific T cell activation through reactive oxygen species signaling. Immunity 38:225–236. https://doi.org/10.1016/j.immuni.2012.10.020

105. Laniewski NG, Grayson JM (2004) Antioxidant treatment reduces expansion and contraction of antigen-specific CD8+ T cells during primary but not secondary viral infection. J Virol 78:11246–11257. https://doi.org/10.1128/JVI.78.20.11246-11257.2004

106. Davies KJ, Quintanilha AT, Brooks GA, Packer L (1982) Free radicals and tissue damage produced by exercise. Biochem Biophys Res Commun 107:1198–1205. https://doi.org/10.1016/s0006-291x(82)80124-1

107. Xia R, Webb JA, Gnall LLM et al (2003) Skeletal muscle sarcoplasmic reticulum contains a NADH-dependent oxidase that generates superoxide. Am J Phys Cell Phys 285:C215–C221. https://doi.org/10.1152/ajpcell.00034.2002

108. Shkryl VM, Martins AS, Ullrich ND et al (2009) Reciprocal amplification of ROS and Ca^{2+} signals in stressed mdx dystrophic skeletal muscle fibers. Pflugers Archiv 458:915–928. https://doi.org/10.1007/s00424-009-0670-2

109. Sakellariou GK, Vasilaki A, Palomero J et al (2013) Studies of mitochondrial and nonmitochondrial sources implicate nicotinamide adenine dinucleotide phosphate oxidase(s) in the increased skeletal muscle superoxide generation that occurs during contractile activity. Antioxid Redox Signal 18:603–621. https://doi.org/10.1089/ars.2012.4623

110. Zhao X, Bey EA, Wientjes FB, Cathcart MK (2002) Cytosolic phospholipase A 2(cPLA 2) regulation of human monocyte NADPH oxidase activity. J Biol Chem 277:25385–25392. https://doi.org/10.1074/jbc.M203630200

111. Kang C, Chung E, Diffee G, Ji LL (2013) Exercise training attenuates aging-associated mitochondrial dysfunction in rat

skeletal muscle: role of PGC-1α. EXG 48:1343–1350. https://doi.org/10.1016/j.exger.2013.08.004

112. Reid MB (2008) Free radicals and muscle fatigue: of ROS, canaries, and the IOC. Free Radic Biol Med 44:169–179. https://doi.org/10.1016/j.freeradbiomed.2007.03.002

113. Vollaard NBJ, Cooper CE, Shearman JP (2006) Exercise-induced oxidative stress in overload training and tapering. Med Sci Sports Exerc 38:1335–1341. https://doi.org/10.1249/01.mss.0000227320.23847.80

114. Sriram S, Subramanian S, Juvvuna PK et al (2014) Myostatin augments muscle-specific ring finger protein-1 expression through an NF-kB independent mechanism in SMAD3 null muscle. Mol Endocrinol 28:317–330. https://doi.org/10.1210/me.2013-1179

115. Witt SH, Granzier H, Witt CC, Labeit S (2005) MURF-1 and MURF-2 target a specific subset of myofibrillar proteins redundantly: towards understanding MURF-dependent muscle ubiquitination. J Mol Biol 350:713–722. https://doi.org/10.1016/j.jmb.2005.05.021

116. Cohen S, Brault JJ, Gygi SP et al (2009) During muscle atrophy, thick, but not thin, filament components are degraded by MuRF1-dependent ubiquitylation. J Cell Biol 185:1083–1095. https://doi.org/10.1083/jcb.200901052

117. Yin F, Sancheti H, Patil I, Cadenas E (2016) Energy metabolism and inflammation in brain aging and Alzheimer's disease. Free Radic Biol Med 100:108–122. https://doi.org/10.1016/j.freeradbiomed.2016.04.200

118. Zhu X-H, Lu M, Lee B-Y et al (2015) In vivo NAD assay reveals the intracellular NAD contents and redox state in healthy human brain and their age dependences. Proc Natl Acad Sci U S A 112:2876–2881. https://doi.org/10.1073/pnas.1417921112

119. Finkel T, Holbrook NJ (2000) Oxidants, oxidative stress and the biology of ageing. Nature 408:239–247. https://doi.org/10.1038/35041687

120. Suárez-Rivero J, Villanueva-Paz M, de la Cruz-Ojeda P et al (2017) Mitochondrial dynamics in mitochondrial diseases. Diseases 5:1–15. https://doi.org/10.3390/diseases5010001

121. Dasuri K, Zhang L, Keller JN (2013) Oxidative stress, neurodegeneration, and the balance of protein degradation and protein synthesis. Free Radic Biol Med 62:170–185. https://doi.org/10.1016/j.freeradbiomed.2012.09.016

122. Zhang J, Perry G, Smith MA et al (2010) Parkinson's disease is associated with oxidative damage to cytoplasmic DNA and RNA in substantia nigra neurons. Am J Pathol 154:1423–1429. https://doi.org/10.1016/S0002-9440(10)65396-5

123. Kruman II, Kumaravel TS, Lohani A et al (2002) Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of Alzheimer's disease. J Neurosci 22:1752–1762

124. Zhang H, Li Q, Graham RK et al (2008) Full length mutant huntingtin is required for altered Ca^{2+} signaling and apoptosis of striatal neurons in the YAC mouse model of Huntington's disease. Neurobiol Dis 31:80–88. https://doi.org/10.1016/j.nbd.2008.03.010

125. Aiken CT, Kaake RM, Wang X, Huang L (2011) Oxidative stress-mediated regulation of proteasome complexes. Mol Cell Proteomics 10(5):R110.006924. https://doi.org/10.1074/mcp.R110.006924

126. Valko M, Leibfritz D, Moncol J et al (2007) Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 39:44–84. https://doi.org/10.1016/j.biocel.2006.07.001

127. Valko M, Rhodes CJ, Moncol J et al (2006) Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact 160:1–40. https://doi.org/10.1016/j.cbi.2005.12.009

128. Sassa A, Kamoshita N, Matsuda T et al (2012) Miscoding properties of 8-chloro-2′-deoxyguanosine, a hypochlorous acid-induced DNA adduct, catalysed by human DNA polymerases. Mutagenesis 28:81–88. https://doi.org/10.1093/mutage/ges056

129. Sheng Z, Oka S, Tsuchimoto D et al (2012) 8-Oxoguanine causes neurodegeneration during MUTYH-mediated DNA base excision repair. J Clin Invest 122:4344–4361. https://doi.org/10.1172/JCI65053

130. Buettner GR (1993) The pecking order of free radicals and antioxidants: lipid peroxidation, alpha-tocopherol, and ascorbate. Arch Biochem Biophys 300:535–543. https://doi.org/10.1006/abbi.1993.1074

131. Hong B-J, Kim J, Jeong H et al (2016) Tumor hypoxia and reoxygenation: the yin and yang for radiotherapy. Radiat Oncol J 34:239–249. https://doi.org/10.3857/roj.2016.02012

132. Kunz M, Ibrahim SM (2003) Molecular responses to hypoxia in tumor cells. Mol Cancer 2:23–13. https://doi.org/10.1186/1476-4598-2-23

133. Liao D, Corle C, Seagroves TN, Johnson RS (2007) Hypoxia-inducible factor-1 is a key regulator of metastasis in a transgenic model of cancer initiation and progression. Cancer Res 67:563–572. https://doi.org/10.1158/0008-5472.CAN-06-2701

134. Waris G, Ahsan H (2006) Reactive oxygen species: role in the development of cancer and various chronic conditions. J Carcinog 5:14. https://doi.org/10.1186/1477-3163-5-14

135. Zuo L, Rose BA, Roberts WJ et al (2014) Molecular characterization of reactive oxygen species in systemic and pulmonary hypertension. Am J Hypertens 27:643–650. https://doi.org/10.1093/ajh/hpt292

136. Szatrowski TP, Nathan CF (1991) Production of large amounts of hydrogen peroxide by human tumor cells. Cancer Res 51:794–798

137. Gorrini C, Gorrini C, Harris IS et al (2013) Modulation of oxidative stress as an anticancer strategy. Nat Rev Drug Discov 12:931–947. https://doi.org/10.1038/nrd4002

138. Gonzalez-Donquiles C, Alonso-Molero J, Fernandez-Villa T et al (2017) The NRF2 transcription factor plays a dual role in colorectal cancer: a systematic review. PLoS One 12:e0177549. https://doi.org/10.1371/journal.pone.0177549

139. Ryoo I-G, Lee S-H, Kwak M-K (2016) Redox modulating NRF2: a potential mediator of cancer stem cell resistance. Oxidative Med Cell Longev 2016:1–14. https://doi.org/10.1155/2016/2428153

140. Kalo E, Kogan-Sakin I, Solomon H et al (2013) Mutant p53 R273H attenuates the expression of phase 2 detoxifying enzymes and promotes the survival of cells with high levels of reactive oxygen species. J Cell Sci 125:5578–5586. https://doi.org/10.1242/jcs.106815

141. Weinberg F, Hamanaka R, Wheaton WW et al (2010) Mitochondrial metabolism and ROS generation are essential for Kras-mediated tumorigenicity. Proc Natl Acad Sci U S A 107:8788–8793. https://doi.org/10.1073/pnas.1003428107

142. Dakubo GD (2006) Altered metabolism and mitochondrial genome in prostate cancer. J Clin Pathol 59:10–16. https://doi.org/10.1136/jcp.2005.027664

143. Jessie BC, Sun CQ, Irons HR et al (2001) Accumulation of mitochondrial DNA deletions in the malignant prostate of patients of different ages. EXG 37:169–174

144. Petros JA, Baumann AK, Ruiz-Pesini E et al (2005) mtDNA mutations increase tumorigenicity in prostate cancer. Proc Natl Acad Sci U S A 102:719–724. https://doi.org/10.1073/pnas.0408894102

145. Schumacker PT (2015) Reactive oxygen species in cancer: a dance with the devil. Cancer Cell 27:156–157. https://doi.org/10.1016/j.ccell.2015.01.007

146. Rabinovitch RC, Samborska B, Faubert B et al (2017) AMPK maintains cellular metabolic homeostasis through regulation of mitochondrial reactive oxygen species. Cell Rep 21:1–9. https://doi.org/10.1016/j.celrep.2017.09.026

147. Hinchy EC, Gruszczyk AV, Willows R et al (2018) Mitochondria-derived ROS activate AMP-activated protein kinase (AMPK) indirectly. J Biol Chem 293:17208–17217. https://doi.org/10.1074/jbc.RA118.002579

148. Hart PC, Mao M, de Abreu ALP et al (2019) MnSOD upregulation sustains the Warburg effect via mitochondrial ROS and AMPK-dependent signalling in cancer. Nat Commun 6:1–14. https://doi.org/10.1038/ncomms7053

149. Tauffenberger A, Fiumelli H, Magistretti PJ (2019) Lactate and pyruvate promote oxidative stress resistance through hormetic ROS signaling. Cell Death Dis 10:1–16. https://doi.org/10.1038/s41419-019-1877-6

150. Zelenka J, Dvořák A, Alán L (2015) L-Lactate protects skin fibroblasts against aging-associated mitochondrial dysfunction via mitohormesis. Oxidative Med Cell Longev 2015:1–14. https://doi.org/10.1155/2015/351698

151. Smith MA, Reid MB (2006) Redox modulation of contractile function in respiratory and limb skeletal muscle. Respir Physiol Neurobiol 151:229–241. https://doi.org/10.1016/j.resp.2005.12.011

152. Andrade FH, Reid MB, Allen DG, Westerblad H (1998) Effect of hydrogen peroxide and dithiothreitol on contractile function of single skeletal muscle fibres from the mouse. J Physiol 509(Pt 2):565–575. https://doi.org/10.1111/j.1469-7793.1998.565bn.x

153. Radák Z, Naito H, Kaneko T et al (2002) Exercise training decreases DNA damage and increases DNA repair and resistance against oxidative stress of proteins in aged rat skeletal muscle. Pflugers Archiv 445:273–278. https://doi.org/10.1007/s00424-002-0918-6

154. Hawley JA, Lessard SJ (2007) Exercise training-induced improvements in insulin action. Acta Physiol 192:127–135. https://doi.org/10.1111/j.1748-1716.2007.01783.x

155. Dodd SL, Gagnon BJ, Senf SM et al (2009) Ros-mediated activation of NF-κB and Foxo during muscle disuse. Muscle Nerve 41:110–113. https://doi.org/10.1002/mus.21526

156. Derbre F, Ferrando B, Gomez-Cabrera MC et al (2012) Inhibition of xanthine oxidase by allopurinol prevents skeletal muscle atrophy: role of p38 MAPKinase and E3 ubiquitin ligases. PLoS One 7:e46668–e46669. https://doi.org/10.1371/journal.pone.0046668

157. Kröller-Schön S, Jansen T, Hauptmann F et al (2012) α1AMP-activated protein kinase mediates vascular protective effects of exercise. Arterioscler Thromb Vasc Biol 32:1632–1641. https://doi.org/10.1161/ATVBAHA.111.243980

158. Ristow M, Zarse K, Oberbach A et al (2009) Antioxidants prevent health-promoting effects of physical exercise in humans. Proc Natl Acad Sci U S A 106:8665–8670. https://doi.org/10.1073/pnas.0903485106

159. Gomez-Cabrera MC, Domenech E, Viña J (2008) Moderate exercise is an antioxidant: upregulation of antioxidant genes by training. Free Radic Biol Med 44:126–131. https://doi.org/10.1016/j.freeradbiomed.2007.02.001

160. Gomez-Cabrera MC, Borras C, Pallardo FV et al (2005) Decreasing xanthine oxidase-mediated oxidative stress prevents useful cellular adaptations to exercise in rats. J Physiol 567:113–120. https://doi.org/10.1113/jphysiol.2004.080564

161. Anderson EJ (2014) The "Goldilocks Zone" from a redox perspective—adaptive vs. deleterious responses to oxidative stress in striated muscle. Front Physiol. https://doi.org/10.3389/fphys.2014.00358/abstract

162. Kalogeris T, Bao Y, Korthuis RJ (2014) Mitochondrial reactive oxygen species: a double edged sword in ischemia/reperfusion vs preconditioning. Redox Biol 2:702–714. https://doi.org/10.1016/j.redox.2014.05.006