

UC Irvine

UC Irvine Previously Published Works

Title

Reactive oxygen species: a breath of life or death?

Permalink

<https://escholarship.org/uc/item/8gk3r693>

Journal

Clinical cancer research : an official journal of the American Association for Cancer Research, 13(3)

ISSN

1078-0432

Authors

Fruehauf, John P
Meyskens, Frank L, Jr

Publication Date

2007-02-01

Peer reviewed

Reactive Oxygen Species: A Breath of Life or Death?

John P. Fruehauf and Frank L. Meyskens, Jr.

Abstract New insights into cancer cell – specific biological pathways are urgently needed to promote development of rationally targeted therapeutics. Reactive oxygen species (ROS) and their role in cancer cell response to growth factor signaling and hypoxia are emerging as verdant areas of exploration on the road to discovering cancer's Achilles heel. One of the distinguishing and near-universal hallmarks of cancer growth is hypoxia. Unregulated cellular proliferation leads to formation of cellular masses that extend beyond the resting vasculature, resulting in oxygen and nutrient deprivation. The resulting hypoxia triggers a number of critical adaptations that enable cancer cell survival, including apoptosis suppression, altered glucose metabolism, and an angiogenic phenotype. Ironically, recent investigations suggest that oxygen depletion stimulates mitochondria to elaborate increased ROS, with subsequent activation of signaling pathways, such as hypoxia inducible factor 1 α , that promote cancer cell survival and tumor growth. Because mitochondria are key organelles involved in chemotherapy-induced apoptosis induction, the relationship between mitochondria, ROS signaling, and activation of survival pathways under hypoxic conditions has been the subject of increased study. Insights into mechanisms involved in ROS signaling may offer novel avenues to facilitate discovery of cancer-specific therapies. Preclinical and clinical evaluation of agents that modify ROS signaling in cancer offers a novel avenue for intervention. This review will cover recent work in ROS-mediated signaling in cancer cells and its potential as a target for developmental therapeutics.

What Are Reactive Oxygen Species and the Redox Balance?

Reactive oxygen species are emerging as critical signaling molecules (1–8). The term reactive oxygen species (ROS) encompasses a wide range of molecules. Free radicals are chemical species containing one or more unpaired electrons. Examples include the hydrogen atom, with one unpaired electron, most transition metal ions, nitric oxide, and oxygen, which has two unpaired electrons (3). The unpaired electrons of oxygen react to form partially reduced highly reactive species that are classified as ROS, including superoxide (O₂⁻), hydrogen peroxide (H₂O₂), hydroxyl radical, and peroxyxynitrite. Various enzyme systems produce ROS, including the mitochondrial electron transport chain, cytochrome P450, lipoxygenase, cyclooxygenase, the NADPH oxidase complex, xanthine oxidase, and peroxisomes (6). Mitochondrial oxygen metabolism is the dominant source of O₂⁻ that results from incomplete coupling of electrons and H⁺ with oxygen in the electron transport chain. Under normoxic conditions, ROS are maintained within narrow boundaries by scavenging systems, as would be expected where

fluxes of such species are involved in cell signaling (8, 9). Redox balance, the ratio between oxidizing and reducing species within the cell, plays a significant role in the regulation of signaling pathways, including kinase and phosphatase activity and gene expression through modulation of transcription factor function (10–12). Redox balance is achieved by various enzyme systems that neutralize toxic oxidants, such as ROS. Superoxide dismutases (SOD) catalyze the conversion of O₂⁻ to H₂O₂, which can then be converted to water by catalase or glutathione (GSH) peroxidase coupled with glutathione reductase. Other relevant scavengers include thioredoxin coupled with thioredoxin reductase, and glutaredoxin, which uses GSH as a substrate. GSH plays a central role in maintaining redox homeostasis, and the GSH to oxidized glutathione ratio provides an estimate of cellular redox buffering capacity (13).

How Do ROS Play a Role in Transformation and Signal Transduction?

ROS-mediated DNA damage has long been thought to play a role in carcinogenesis initiation and malignant transformation (Fig. 1A; ref. 14). Hydroxyl radicals, for example, react with pyrimidines, purines, and chromatin protein, resulting in base modifications, genomic instability, and alterations in gene expression. Mitochondrial DNA is a particularly vulnerable target because of its proximity to the electron transport chain constituents. ROS-mediated mutations in mitochondrial DNA have recently emerged as an important variable in carcinogenesis (15). Pathologic sources of transforming ROS include chronic inflammation secondary to infections or chronic chemical irritants (tobacco smoke, asbestos; refs. 16, 17). Transformed cells commonly lack cell cycle checkpoints and

Authors' Affiliation: Departments of Medicine and Biological Chemistry, Chao Family Comprehensive Cancer Center, University of California, Irvine, Orange, California

Received 8/22/06; accepted 8/25/06.

Requests for reprints: John P. Fruehauf, Hematology/Oncology, University of California, Irvine, Cancer Center, Building 55, Room 321, 101 City Drive Cancer Center, Orange, CA 92668. Phone: 714-456-6310; Fax: 714-456-7668; E-mail: jfruehau@uci.edu.

© 2007 American Association for Cancer Research.
doi:10.1158/1078-0432.CCR-06-2082

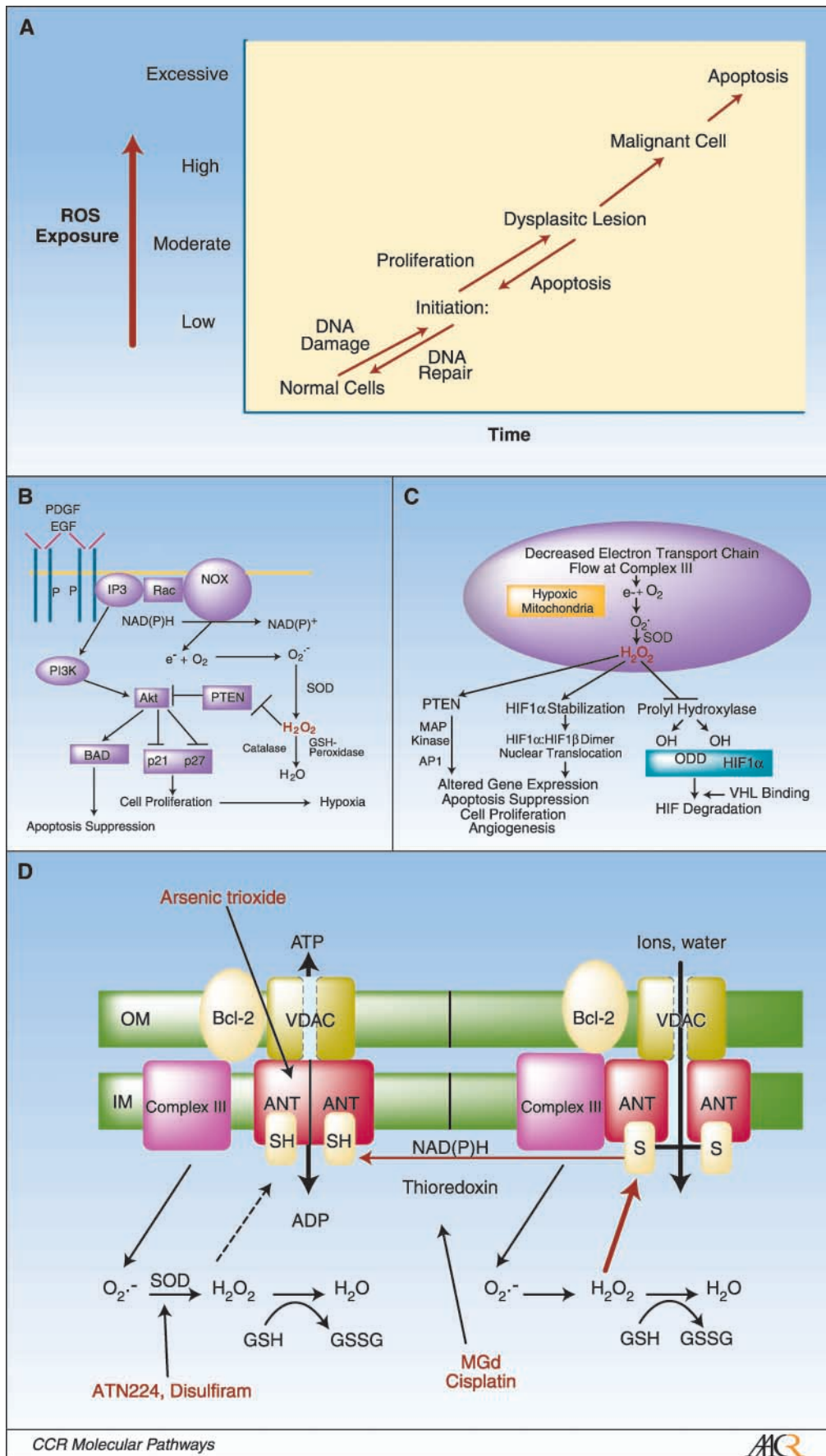


Fig. 1. A, chronic ROS exposure is carcinogenic. Excess levels are toxic to cancer cells. B, tyrosine kinase receptor signaling is amplified by ROS via inhibition of PTEN, stimulating cell proliferation and suppressing apoptosis. IP3, inositol 1,4,5-trisphosphate. EGF, epidermal growth factor. C, hypoxic mitochondria signal via superoxide and hydrogen peroxide to stabilize HIF1 α and activate mitogen-activated protein (MAP) kinase signaling, promoting cell proliferation, apoptosis suppression, and angiogenesis. AP1, activator protein-1; ODD, oxygen-dependent degradation domain. VHL, von Hippel-Lindau. D, targeting ROS-sensitive components of the mitochondrial permeability pore offers a new avenue for therapeutic intervention. OM, outer membrane; IM, inner membrane; GSSG, oxidized glutathione. Fig. 1D adapted with permission from Armstrong (59).

overexpress oncogene growth factors and their tyrosine kinase receptors that drive cell proliferation, ultimately leading to tumor formation and chronic hypoxia (18). Several tyrosine kinase receptors have been shown to signal via ROS-dependent mechanisms (19, 20). Both the epidermal growth factor receptor and platelet-derived growth factor receptor signal in part through H_2O_2 generation (Fig. 1B). Ligand-induced receptor dimerization activates phosphatidylinositol 3-kinase, resulting in inositol 1,4,5-triphosphate activation of Rac, which, in turn, activates the NADPH oxidase complex to produce superoxide and downstream signaling through O_2^- and H_2O_2 . H_2O_2 modulates signal transduction through its oxidation of the catalytic cysteine of protein tyrosine phosphatases, such as PTEN, preventing inactivation of tyrosine kinase signaling through activator protein-1 and Akt (21–23). H_2O_2 -mediated inhibition of protein phosphatases contributes to both cellular proliferation and apoptosis suppression and links oncogene overexpression, a hallmark of many cancers, with ROS-mediated signaling (24). Oncogene growth factor activation and signal transduction drives cell proliferation beyond the carrying capacity of the resting vasculature. As few as 300 malignant cells are adequate for the production of a hypoxic environment that turns on angiogenesis (25). It is not surprising then that Akt activation by ROS can also support tumor cell survival under hypoxic conditions by increasing the translation of hypoxia inducible factor 1 α (HIF1 α ; ref. 26).

What Is the Role of HIF Stabilization in Hypoxia?

Tumor survival in a hypoxic environment requires a coordinated adaptive response. Identification of mechanisms of oxygen sensing and its effect on cellular adaptations to hypoxia has been a critical task facing tumor biologists (27, 28). Initial studies suggested that HIF1 α was a central regulator of hypoxic response (29–32). More than 70 genes are under its transcriptional control to facilitate survival under low oxygen pressures (29). HIF1 α is constitutively expressed, but its half life is extremely short due to rapid hydroxylation by dioxygen, oxaloglutarate, and iron-dependent prolyl 4-hydroxylases (PHD 1, 2, and 3), located in the nucleus, cytoplasm, or both, respectively. After PHD-mediated hydroxylation of Pro⁵⁶⁴ and Pro⁴⁰² in its oxygen-dependent degradation domain, HIF1 α complexes with the β -domain of von Hippel-Lindau tumor suppressor protein, a recognition component of an E3 ubiquitin-protein ligase complex, and undergoes rapid NH_2 - and $COOH$ -terminal ubiquitination and proteolysosomal degradation (30, 31). Under normoxic conditions, the half-life of HIF1 α is <5 min (31). Based on the oxygen requirements for PHD-mediated hydroxylation, it was initially postulated that this was the key oxygen sensor protein (27). However, inhibition of PHD does not occur until oxygen levels decrease below 5%, with maximal inhibition not seen until near-complete anoxia (32). Recent studies suggest that various oxygen species can promote HIF1 α stabilization by inhibiting PHD activity, including nitric oxide and ROS, some of which may be of mitochondrial origin (33–35).

What Is the Role of Mitochondrial H_2O_2 in HIF Stabilization?

Based on the central role of oxygen in oxidative phosphorylation, it is not surprising that mitochondria can signal a cellular

response when oxygen levels decrease (Fig. 1C; refs. 34, 35). Under hypoxic conditions, mitochondria participate in a ROS burst generated at complex III of the electron transport chain (36). When the partial pressure of oxygen is reduced, mitochondrial electron transfer from ubiquinol to cytochrome c_1 by the Rieske iron-sulfur protein is delayed, allowing electrons to bind to molecular oxygen, forming O_2^- (36). Superoxide is then converted to H_2O_2 by SOD (Mn-SOD in the mitochondrial matrix and Cu,Zn-SOD in the mitochondrial intermembrane space and cytosol). The resulting H_2O_2 efflux into the cytosol exerts an inhibitory effect on PHD activity, allowing HIF1 α to accumulate, dimerize with HIF1 β , and translocate into the nucleus where it modulates the expression of genes that favor survival under hypoxic conditions (Fig. 1C; ref. 29). Support for the role of mitochondrial ROS in HIF1 α stabilization comes from work which shows that HIF1 α stabilization can be blocked under hypoxic conditions if ROS production is abrogated in mitochondria that lack cytochrome c or that have been treated with small interfering RNA to knock down the Rieske protein (37, 38). However, HIF1 α stabilization under anoxic conditions is independent on mitochondrial ROS (36). Although the mechanism whereby H_2O_2 inhibits PHD activity has yet to be elucidated, current efforts are focused on PHD iron oxidation (39).

Can Modulation of ROS Be Therapeutic?

ROS are increased in malignant cells in part as a result of oncogene signaling via the NADPH oxidase complex and by hypoxia-related mitochondrial ROS. Increased oxidant levels contribute to enhanced cell proliferation and apoptosis suppression (Fig. 1B and C). Two independent therapeutic strategies targeting these pathways are possible. One point of attack would be to increase ROS scavenging, thereby dampening H_2O_2 signaling and depressing tumor growth. An opposite approach would be to treat cells with agents that interfere with ROS scavenging, resulting in excess ROS that would trigger apoptosis (Fig. 1D; refs. 9, 40–42). Evidence to support a strategy to enhance scavenging is provided by studies showing that overexpression of SOD, glutathione peroxidase, or catalase decreased tumor growth *in vitro* and *in vivo* in mouse models (43–46). Although there are no specific agents available that selectively induce these enzyme systems, nutraceutical preparations are under study that show some promise (47). In opposition to increased scavenging are therapeutic maneuvers that interfere with ROS removal, leading to an accumulation of excess ROS. High levels of ROS can cause apoptosis by triggering mitochondrial permeability transition pore opening and release of proapoptotic factors (Fig. 1D; ref. 48).

How Does the Mitochondria Control Apoptosis?

The mitochondrial permeability transition pore complex is a highly regulated multimeric channel consisting of an inner membrane segment, the adenine nucleotide translocase (ANT), which imports ADP and exports ATP, cyclophilin D, intermembrane creatine kinase, and the outer membrane voltage dependent ion channel (VDAC, porin). Chemotherapy agents modulate pore opening primarily by triggering DNA damage response pathways at cell cycle checkpoints (18). DNA repair pathways are coupled with apoptosis effectors to ensure that

irreparable damage will not be passed down to daughter cells. Drug-induced apoptosis results when cytosolic concentrations of pore opening proteins, such as Bax and Bak, increase above a critical threshold and are targeted to destabilize VDAC by chaperones such as Bid and Bim. VDAC destabilization increases ROS generation and promotes ion influx and ultimate mitochondrial membrane rupture, causing the release of the proapoptotic protein group, including cytochrome *c*, apoptosis-inducing factor, Smac/Diablo, procaspases, and Endo G (49, 50). On the other hand, hexokinases I and II (up-regulated by HIF), Bcl-2, Bid, and BCL-X_L (up-regulated by tyrosine kinase receptor and ROS signaling) exert antiapoptotic effects by stabilizing VDAC configuration (51, 52).

Are Mitochondrial Permeability Pores and Apoptosis Regulated by ROS?

In addition to attack by pore-destabilizing proteins, VDAC, which may regulate O₂⁻ flux from the mitochondria to the cytosol, is susceptible to superoxide-mediated mitochondrial permeability transition pore opening (53–55). Thus, VDAC can be a target of ROS buildup to stimulate apoptosis. The inner mitochondrial protein, ANT, is also a target of ROS modulation by virtue of its redox-sensitive cysteines, providing an additional mechanism by which drug-induced GSH depletion and loss of ROS scavenging may cause apoptosis (Fig. 1D; ref. 56). ANT contains three reduced cysteine residues in the 57, 160, and 257 positions. Oxidation-induced disulfide cross-linking of Cys¹⁶⁰ with Cys²⁵⁷ results in mitochondrial permeability transition pore complex opening (57). Cross-linking of these Cys residues alters ANT conformation, inhibiting its ability to bind nucleotides and allowing calcium entry. Increased calcium is postulated to promote a cyclophilin D-ANT complex to form, which induces pore opening, leading to apoptosis (58). Glutathione prevents this cross-linking, whereas oxidized glutathione may mediate disulfide cross-link formation between Cys¹⁶⁰ with Cys²⁵⁷, resulting in apoptosis (59, 60). This disulfide can be reduced by thioredoxin coupled to thioredoxin reductase or by GSH coupled to glutathione reductase, reversing pore opening (61). ROS scavenging in the mitochondria is therefore required to promote a redox balance that maintains ANT in an active form that binds adenine nucleotides at both high- and low-affinity sites, preventing calcium from reaching cyclophilin D, thereby preventing pore opening.

What Drugs Are Available to Inhibit ROS Scavenging?

Therapeutic strategies that promote ROS accumulation and apoptosis have been explored based on the availability of drugs that interfere with scavenging (Fig. 1D; refs. 42, 62, 63). Agents that deplete GSH, such as buthionine sulfoximine and arsenic trioxide, have shown *in vitro* and clinical activity

(56, 64–67). Arsenic trioxide may act directly on VDAC to induce pore opening (68). Inhibition of Cu,Zn-SOD by agents that chelate Cu, such as disulfiram and ATN224, have shown *in vitro* and *in vivo* clinical activity (69–72). Both buthionine sulfoximine and disulfiram were found by our group to be active against melanoma *in vitro* (65, 69). Melanoma cells are postulated to contain excess levels of ROS secondary to dysregulated melanin synthesis (42, 65). Under oxidizing conditions, melanin is converted from an antioxidant to a prooxidant macromolecule (73).

Inhibition of thioredoxin, which maintains ANT in a reduced state, is another potential target for disruption of ROS scavenging (74). Flavanols, such as quercetin, are capable of causing cancer cell death via inhibition of thioredoxin, and their activity is enhanced by superoxide anions (75). A new compound, motexafin gadolinium, which was initially developed as a radiosensitizer, is an effective inhibitor of thioredoxin, and is currently undergoing phase III clinical trials (76, 77). Motexafin gadolinium is relatively tumor specific based on its porphyrin-like structure that is preferentially taken up by cancer cells. It induces oxidative stress by a mechanism of futile redox cycling (due to transfer of electrons from reduced substrates to O₂⁻ to produce ROS). A wide spectrum of critical reducing proteins, including GSH and reduced thioredoxin, are oxidized by motexafin gadolinium. Motexafin gadolinium not only inhibits thioredoxin but also converts this scavenger to an ROS generator, which further contributes to apoptosis induction (78). Of note, conventional chemotherapy agents can inhibit thioredoxin, including melphalan, carmustine, cisplatin, and oxaliplatin (79). Thus, combining these agents in synergistic combinations may prove to be the most useful approach. To date, the toxicity of these newer ROS-targeted agents has been tolerable.

In summary, ROS species are involved in carcinogenesis, promotion of transformed cell growth, stabilization of HIF1 α to promote angiogenesis, and regulation of mitochondrial apoptotic programs. Scavenging of H₂O₂ in transformed cells can effectively diminish tumor growth by blocking growth factor receptor signaling and by preventing peroxide-mediated stabilization of HIF1 α . Although inhibition of redox signaling through enhanced ROS scavenging has been attempted as a chemoprevention strategy early in the transformation process, few studies have successfully showed proof of this principle for patients with advanced disease (80). It is unlikely that abrogation of ROS signaling can significantly affect patient outcomes due to the complexity of redundant pathways supporting cancer growth (18). On the other hand, enhancing mitochondrial ROS production to trigger apoptosis presents an attractive target because this organelle controls cellular decisions to live or die. Cancer-specific therapies may ultimately benefit from the increased ROS produced by hypoxic mitochondria. Through the inhibition of ROS scavenging, increased levels of ROS can be seen as the Achilles' heel of cancer cell metabolism. The next decade should reveal the truth or consequences of this approach.

References

1. Kamata H, Hirata H. Redox regulation of cellular signaling. *Cell Signal* 1999;11:1–14.
2. Ueda S, Masutani H, Nakamura H, Tanaka T, Ueno M, Yodoi J. Redox control of cell death. *Antioxid Redox Signal* 2002;4:405–14.
3. Halliwell B. Reactive oxygen species in living systems: source, biochemistry, and role in human disease. *Am J Med* 1991;91:14–22S.
4. Kieran MW, Folkman J, Heymach J. Angiogenesis inhibitors and hypoxia. *Nat Med* 2003;9:822–3.
5. Harris AL. Hypoxia—a key regulatory factor in tumour growth. *Nat Rev Cancer* 2002;2:38–47.
6. Inoue M, Sato EF, Nishikawa M, et al. Mitochondrial generation of reactive oxygen species and its role in aerobic life. *Curr Med Chem* 2003;10:2495–505.

7. Pouyssegur J, Dayan F, Mazure NM. Hypoxia signaling in cancer and approaches to enforce tumour regression. *Nature* 2006;441:437–43.
8. Linnane AW, Eastwood H. Cellular redox regulation and prooxidant signaling systems: a new perspective on the free radical theory of aging. *Ann N Y Acad Sci* 2006;1067:47–55.
9. Kinnula VL, Crapo JD. Superoxide dismutases in malignant cells and human tumors. *Free Radic Biol Med* 2004;36:718–44.
10. Thannickal VJ, Fanburg BL. Reactive oxygen species in cell signaling. *Am J Physiol Lung Cell Mol Physiol* 2000;279:L1005–28.
11. Sen CK. Cellular thiols and redox-regulated signal transduction. *Curr Top Cell Regul* 2000;36:1–30.
12. Biswas S, Chida AS, Rahman I. Redox modifications of protein-thiols: emerging roles in cell signaling. *Biochem Pharmacol* 2006;71:551–64.
13. Schafer FQ, Buettner GR. Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple. *Free Radic Biol Med* 2001;30:1191–212.
14. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem Biol Interact* 2006;160:1–40. Epub 2006.
15. Singh KK. Mitochondrial damage checkpoint, aging, and cancer. *Ann N Y Acad Sci* 2006;1067:182–90.
16. Sikka SC. Role of oxidative stress response elements and antioxidants in prostate cancer pathobiology and chemoprevention—a mechanistic approach. *Curr Med Chem* 2003;10:2679–92.
17. Knaapen AM, Borm PJ, Albrecht C, Schins RP. Inhaled particles and lung cancer. Part A: Mechanisms. *Int J Cancer* 2004;109:799–809.
18. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000;100:57–70.
19. Sundaresan M, Yu ZX, Ferrans VJ, Irani K, Finkel T. Requirement for generation of H₂O₂ for platelet-derived growth factor signal transduction. *Science* 1995;270:296–9.
20. BaeYS, Kang SW, Seo MS, et al. Epidermal growth factor (EGF)-induced generation of hydrogen peroxide. Role in EGF receptor-mediated tyrosine phosphorylation. *J Biol Chem* 1997;272:217–21.
21. Groen A, Lemeer S, van der Wijk T, et al. Differential oxidation of protein-tyrosine phosphatases. *J Biol Chem* 2005;280:10298–304.
22. Leslie NR, Bennett D, Lindsay YE, Stewart H, Gray A, Downes CP. Redox regulation of PI3-kinase signaling via inactivation of PTEN. *EMBO J* 2003;22:5501–10.
23. Wang X, McCullough KD, Franke TF, Holbrook NJ. Epidermal growth factor receptor-dependent Akt activation by oxidative stress enhances cell survival. *J Biol Chem* 2000;275:14624–31.
24. Benhar M, Engelberg D, Levitzki A. ROS, stress-activated kinases and stress signaling in cancer. *EMBO Rep* 2002;3:420–5.
25. Li CY, Shan S, Huang Q, et al. Initial stages of tumor cell-induced angiogenesis: evaluation via skin window chambers in rodent models. *J Natl Cancer Inst* 2000;92:143–7.
26. Pore N, Jiang Z, Shu HK, Bernhard E, Kao GD, Maiti A. Akt1 activation can augment hypoxia-inducible factor-1 α expression by increasing protein translation through a mammalian target of rapamycin-independent pathway. *Mol Cancer Res* 2006;4:471–9.
27. Pugh CW. Oxygen sensing in cancer. *Ann Med* 2003;35:380–90.
28. Verma A. Oxygen-sensing in tumors. *Curr Opin Clin Nutr Metab Care* 2006;9:366–78.
29. Semenza GL, Shimoda LA, Prabhakar NR. Regulation of gene expression by HIF-1. *Novartis Found Symp* 2006;272:2–8.
30. Maxwell PH, Wiesener MS, Chang GW, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* 1999;399:271–5.
31. Huang LE, Gu J, Schau M, Bunn HF. Regulation of hypoxia-inducible factor 1 α is mediated by an O₂-dependent degradation domain via the ubiquitin-proteasome pathway. *Proc Natl Acad Sci U S A* 1998;95:7987–92.
32. Jiang BH, Semenza GL, Bauer C, Marti HH. Hypoxia-inducible factor 1 levels vary exponentially over a physiologically relevant range of O₂ tension. *Am J Physiol* 1996;271:C1172–80.
33. Metzzen E, Zhou J, Jelkmann W, Fandrey J, Brune B. Nitric oxide impairs normoxic degradation of HIF-1 α by inhibition of prolyl hydroxylases. *Mol Biol Cell* 2003;14:3470–81.
34. Bell EL, Emerling BM, Chandel NS. Mitochondrial regulation of oxygen sensing. *Mitochondrion* 2005;5:322–32.
35. Wallace DC. Mitochondria and cancer: Warburg addressed. *Cold Spring Harb Symp Quant Biol* 2005;70:363–74.
36. Guzy RD, Schumacker PT. Oxygen sensing by mitochondria at complex III: The paradox of increased ROS during hypoxia. *Exp Physiol* 2006;91:807–19.
37. Mansfield KD, Guzy RD, Pan Y, et al. Mitochondrial dysfunction resulting from loss of cytochrome *c* impairs cellular oxygen sensing and hypoxic HIF- α activation. *Cell Metab* 2005;1:393–9.
38. Brunelle JK, Bell EL, Quesada NM, et al. Oxygen sensing requires mitochondrial ROS but not oxidative phosphorylation. *Cell Metab* 2005;1:409–14.
39. Kietzmann T, Gorkach A. Reactive oxygen species in the control of hypoxia-inducible factor-mediated gene expression. *Semin Cell Dev Biol* 2005;16:474–86.
40. Fleury C, Mignotte B, Vayssières JL. Mitochondrial reactive oxygen species in cell death signaling. *Biochimie* 2002;84:131–41.
41. Le Bras M, Clement MV, Pervaiz S, Brenner C. Reactive oxygen species and the mitochondrial signaling pathway of cell death. *Histol Histopathol* 2005;20:205–19.
42. Meyskens FL, Jr., Farmer P, Fruehauf JP. Redox regulation in human melanocytes and melanoma. *Pigment Cell Res* 2001;14:148–54.
43. Ough M, Lewis A, Zhang Y, et al. Inhibition of cell growth by overexpression of manganese superoxide dismutase (MnSOD) in human pancreatic carcinoma. *Free Radic Res* 2004;38:1223–33.
44. Venkataraman S, Jiang X, Weydert C, et al. Manganese superoxide dismutase overexpression inhibits the growth of androgen-independent prostate cancer cells. *Oncogene* 2005;24:77–89.
45. Liu J, Du J, Zhang Y, et al. Suppression of the malignant phenotype in pancreatic cancer by overexpression of phospholipid hydroperoxide glutathione peroxidase. *Hum Gene Ther* 2006;17:105–16.
46. Finch JS, Tome ME, Kwei KA, Bowden GT. Catalase reverses tumorigenicity in a malignant cell line by an epidermal growth factor receptor pathway. *Free Radic Biol Med* 2006;40:863–75.
47. Nelson SK, Bose SK, Grunwald GK, Myhill P, McCord JM. The induction of human superoxide dismutase and catalase *in vivo*: a fundamentally new approach to antioxidant therapy. *Free Radic Biol Med* 2006;40:341–7.
48. Brenner C, Grimm S. The permeability transition pore complex in cancer cell death. *Oncogene* 2006;25:4744–56.
49. Faustin B, Rossignol R, Rocher C, Benard G, Malgat M, Letellier T. Mobilization of adenine nucleotide translocators as molecular bases of the biochemical threshold effect observed in mitochondrial diseases. *J Biol Chem* 2004;279:20411–21.
50. Bauer MK, Schubert A, Rocks O, Grimm S. Adenine nucleotide translocase-1, a component of the permeability transition pore, can dominantly induce apoptosis. *J Cell Biol* 1999;147:1493–502.
51. Scorrano L, Korsmeyer SJ. Mechanisms of cytochrome *c* release by proapoptotic BCL-2 family members. *Biochem Biophys Res Commun* 2003;304:437–44.
52. Shoshan-Barmatz V, Israelson A, Brdiczka D, Sheu SS. The voltage-dependent anion channel (VDAC): function in intracellular signalling, cell life and cell death. *Curr Pharm Des* 2006;12:2249–70.
53. Madesh M, Hajnoczky G. VDAC-dependent permeabilization of the outer mitochondrial membrane by superoxide induces rapid and massive cytochrome *c* release. *J Cell Biol* 2001;155:1003–15.
54. Han D, Antunes F, Canali R, Rettori D, Cadenas E. Voltage-dependent anion channels control the release of the superoxide anion from mitochondria to cytosol. *J Biol Chem* 2003;278:5557–63.
55. Garrido C, Galluzzi L, Brunet M, Puig PE, Didelot C, Kroemer G. Mechanisms of cytochrome *c* release from mitochondria. *Cell Death Differ* 2006;13:1423–33.
56. Li JJ, Tang Q, Li Y, et al. Role of oxidative stress in the apoptosis of hepatocellular carcinoma induced by combination of arsenic trioxide and ascorbic acid. *Acta Pharmacol Sin* 2006;27:1078–84.
57. Costantini P, Belzacq AS, Vieira HL, et al. Oxidation of a critical thiol residue of the adenine nucleotide translocator enforces Bcl-2-independent permeability transition pore opening and apoptosis. *Oncogene* 2000;19:307–14.
58. Halestrap AP, Clarke SJ, Javadov SA. Mitochondrial permeability transition pore opening during myocardial reperfusion—a target for cardioprotection. *Cardiovasc Res* 2004;61:372–85.
59. Armstrong JS, Jones DP. Glutathione depletion enforces the mitochondrial permeability transition and causes cell death in Bcl-2 overexpressing HL60 cells. *FASEB J* 2002;16:1263–5.
60. Imai H, Koumura T, Nakajima R, Nomura K, Nakagawa Y. Protection from inactivation of the adenine nucleotide translocator during hypoglycaemia-induced apoptosis by mitochondrial phospholipid hydroperoxide glutathione peroxidase. *Biochem J* 2003;371:799–809.
61. Wudarczyk J, Debska G, Lenartowicz E. Relation between the activities reducing disulfides and the protection against membrane permeability transition in rat liver mitochondria. *Arch Biochem Biophys* 1996;327:215–21.
62. Estrela JM, Ortega A, Obrador E. Glutathione in cancer biology and therapy. *Crit Rev Clin Lab Sci* 2006;43:143–81.
63. Chen X, Carystinos GD, Batist G. Potential for selective modulation of glutathione in cancer chemotherapy. *Chem Biol Interact* 1998;111–2:263–75.
64. Friesen C, Kiess Y, Debatin KM. A critical role of glutathione in determining apoptosis sensitivity and resistance in leukemia cells. *Cell Death Differ* 2004;11:573–85.
65. Fruehauf JP, Zonis S, al-Bassam M, et al. Melanin content and downregulation of glutathione S-transferase contribute to the action of L-buthionine-S-sulfoximine on human melanoma. *Chem Biol Interact* 1998;111–2:277–305.
66. Bailey HH, Mulcahy RT, Tutsch KD, et al. Phase I clinical trial of intravenous L-buthionine sulfoximine and melphalan: an attempt at modulation of glutathione. *J Clin Oncol* 1994;12:194–205.
67. Tchounwou PB, Yedjou CG, Dorsey WC. Arsenic trioxide-induced transcriptional activation of stress genes and expression of related proteins in human liver carcinoma cells (HepG2). *Cell Mol Biol* 2003;49:1071–9.
68. Zheng Y, Shi Y, Tian C, et al. Essential role of the voltage-dependent anion channel (VDAC) in mitochondrial permeability transition pore opening and cytochrome *c* release induced by arsenic trioxide. *Oncogene* 2004;23:1239–47.
69. Cen D, Brayton D, Shahandeh B, Meyskens FL, Jr., Farmer PJ. Disulfiram facilitates intracellular Cu uptake and induces apoptosis in human melanoma cells. *J Med Chem* 2004;47:6914–20.
70. Brar SS, Grigg C, Wilson KS, et al. Disulfiram inhibits activating transcription factor/cyclic AMP-responsive element binding protein and human melanoma growth in a metal-dependent manner *in vitro*, in mice and in a patient with metastatic disease. *Mol Cancer Ther* 2004;3:1049–60.
71. Juarez JC, Betancourt O, Jr., Pirie-Shepherd SR, et al. Copper binding by tetrathiomolybdate attenuates

- angiogenesis and tumor cell proliferation through the inhibition of superoxide dismutase 1. *Clin Cancer Res* 2006;12:4974–82.
72. Campbell RA, Gordon MS, Betancourt O, et al. ATN-224, an orally available small molecule inhibitor of SOD1, inhibits multiple signaling pathways associated with myeloma progression and has antitumor activity in a murine model of refractory myeloma growth [abstract 4859]. *Proc Am Assoc Cancer Res* 2006.
73. Meyskens FL, Jr., Farmer PJ, Anton-Culver H. Etiologic pathogenesis of melanoma: a unifying hypothesis for the missing attributable risk. *Clin Cancer Res* 2004;10:2581–3.
74. Biaglow JE, Miller RA. The thioredoxin reductase/thioredoxin system: novel redox targets for cancer therapy. *Cancer Biol Ther* 2005;4:6–13.
75. Lu J, Papp LV, Fang J, Rodriguez-Nieto S, Zhivotovsky B, Holmgren A. Inhibition of mammalian thioredoxin reductase by some flavonoids: implications for myricetin and quercetin anticancer activity. *Cancer Res* 2006;66:4410–8.
76. Young SW, Qing F, Harriman A, et al. Gadolinium(III) texaphyrin: a tumor selective radiation sensitizer that is detectable by MRI. *Proc Natl Acad Sci U S A* 1996;93:6610–5. Erratum in: *Proc Natl Acad Sci U S A* 1999;96:2569.
77. Evens AM. Motexafin gadolinium: a redox-active tumor selective agent for the treatment of cancer. *Curr Opin Oncol* 2004;16:576–80.
78. Hashemy SI, Ungerstedt JS, Avval FZ, Holmgren A. Motexafin gadolinium, a tumor-selective drug targeting thioredoxin reductase and ribonucleotide reductase. *J Biol Chem* 2006;281:10691–7.
79. Witte AB, Anestal K, Jerremalm E, Ehrsson H, Arner ES. Inhibition of thioredoxin reductase but not of glutathione reductase by the major classes of alkylating and platinum-containing anticancer compounds. *Free Radic Biol Med* 2005;39:696–703.
80. Meyskens FL, Szabo E. Diet and cancer: the disconnect between epidemiology and randomized clinical trials. *Cancer Epidemiol Biomarkers Prev* 2005;14:1366–9.

Reactive Oxygen Species: A Breath of Life or Death?

John P. Fruehauf and Frank L. Meyskens, Jr.

Clin Cancer Res 2007;13:789-794.

Updated version Access the most recent version of this article at:
<http://clincancerres.aacrjournals.org/content/13/3/789>

Cited Articles This article cites by 77 articles, 26 of which you can access for free at:
<http://clincancerres.aacrjournals.org/content/13/3/789.full.html#ref-list-1>

Citing articles This article has been cited by 48 HighWire-hosted articles. Access the articles at:
<http://clincancerres.aacrjournals.org/content/13/3/789.full.html#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.